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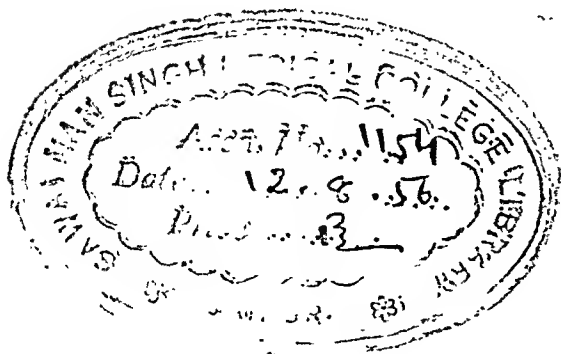
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# The American Heart Journal

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## Original Communications

### SOME IMMEDIATE CAUSES OF CARDIAC INFARCTION

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**I**S CARDIAC infarction a fortuitous occurrence, or are there specific, recognizable circumstances that precede the cardiac damage? This is an old problem, and one that is still giving rise to much discussion. Some years ago, Fitzhugh and Hamilton<sup>1</sup> collected a series of cases of coronary thrombosis in which it appeared that the attacks were brought on by some unusual event. In the intervening years we have learned a good deal about coronary artery disease. We know that cardiac infarction can take place without coronary thrombosis.<sup>2</sup> We understand something about the role played by hemorrhages into the coronary arterial wall in causing closure of the coronary lumen. We have learned to recognize the so-called premonitory symptoms of cardiac infarction and realize that changes in the coronary circulation which eventually lead to complete arterial occlusion may develop over a period of days, possibly weeks.

Much of the confusion that has arisen is due to the lack of differentiation between attacks of angina pectoris, coronary occlusion, and coronary insufficiency. By angina pectoris we understand the particular type of heart pain which is usually induced by exertion or excitement, is of short duration, and is not followed by permanent myocardial damage. Yet it is now accepted that every attack of angina pectoris is due to transient coronary insufficiency, and that an electrocardiogram taken during an attack of pain may show changes indicative of heart muscle damage; these changes disappear promptly after the attack. We are accustomed to associate the concept of coronary occlusion with dramatic and severe symptoms, namely, shock, a fall in blood pressure, fever, and heart failure, with progressive electrocardiographic changes. As a matter of fact, it is often difficult to ascertain whether an attack of heart pain represents simple angina or coronary occlusion.

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This has been brought out very forcibly by the recent work of Blumgart and Schlesinger.<sup>3</sup> In painstaking autopsy studies, using a special method developed by Schlesinger, they were able to show that in all cases in which the subject had suffered from simple angina pectoris, without complicating hypertension or valvular disease, and with no symptoms suggesting cardiac infarction, there were occlusions of several coronary arteries, but there was no significant scarring of the heart muscle. In these cases the development of the arterial disease was so slow that there was time for the establishment of an adequate collateral circulation, so that, when one of the coronary arteries was occluded, infarction of the myocardium did not take place. Blumgart pointed out that, when patients who were previously well suddenly develop angina pectoris, particularly at rest, one must suspect coronary narrowing or occlusion, even if none of the signs of cardiac infarction appear.

Very commonly we encounter a patient who tells us that he has had typical angina pectoris for many months and that he has never been incapacitated by any severe attack that compelled him to go to bed. Yet, if one says to such a patient, "Do you remember the very first time you had this pain, and did the initial attack differ in any way from the subsequent ones?" he is very likely to answer something like this (I cite two cases from my files): "Oh, yes, I remember that I was at a New Year's party and drank too much, ate too much, and danced a good deal. While dancing, I suddenly experienced substernal pain, broke out into a sweat, and had to sit down, but the symptoms disappeared in about fifteen minutes. I then went home and slept it off and returned to work the next day. Ever since, walking a few blocks has provoked similar symptoms."

Another man will tell you that the first attack occurred while he was shoveling snow on a cold winter day, and that the pain compelled him to stop, go into the house, and rest, but that it did not compel him to be away from his work.

Many, but not all, of these patients, when examined subsequently, show electrocardiographic changes which are indicative of myocardial damage.

It is my conviction that such patients, who are ordinarily regarded as having simple angina pectoris, have at the outset experienced organic damage to one of their coronary arteries, leading either to permanent narrowing or occlusion of the vessel.

Blumgart and his associates called attention to persons who have prolonged attacks of classical anginal pain which are not followed by fever or other evidence of infarction, and show no infarction post mortem. Such cases they ascribe to coronary failure which causes a reversible myocardial ischemia. They point out that such attacks are occasionally coincident with increased demands on the heart and that

they may be provoked by a paroxysmal abnormal rhythm, emotional upsets, or exertion. At times they may follow sudden insufficiency of the coronary flow secondary to shock or hemorrhage. Fresh infarcts may occur without fresh coronary occlusion when the coronary failure is prolonged to a point where myocardial necrosis takes place.

The demonstration of the frequency with which coronary occlusion and consequent cardiac infarction result from hemorrhage into the arterial wall has thrown new light on some forms of coronary occlusion.<sup>4</sup> These pathologic studies offer a possible explanation for certain cases of traumatic cardiac infarction and for the sudden onset of symptoms of angina pectoris. They also could account for gradual coronary occlusions that may take days to become complete. There may be a gradual growth of the hematoma in the arterial wall, or gradual formation of an intra-arterial thrombus over the site of the hemorrhage into the arterial wall.<sup>5</sup>

I wish to present a series of cases of cardiac infarction in which the sequence of events suggested a direct connection between the cardiac infarction and some concrete, antecedent happening. These are not rare or isolated cases. They were culled from many that I have encountered in my practice. Indeed, these relationships occur with such frequency that I, for one, have become convinced of their causal connection.

#### NONPENETRATING CHEST INJURIES

I do not propose to dwell long on nonpenetrating injuries of the chest that produce myocardial damage. The mechanism of this is now generally understood, and I have summarized the evidence in an earlier paper.<sup>2a</sup> Since that time, Warburg<sup>6</sup> and Barber<sup>7</sup> have published additional cases. The following is still another case.

CASE 1.—A man, aged 40, while driving his car, collided head on with a truck. He became momentarily unconscious. When he awoke, he was lying over the steering wheel, which had been bent forward so that it rested against the windshield. He clambered out of the car, collapsed, and felt a tightness across the anterior part of the chest. He was driven to a doctor's office. No bruises were found on his chest, and no ribs were broken. He was then driven to his office, about 6 miles, and then home, another 7 miles. He stayed in bed two weeks. During this period he was constantly short of breath and felt a tightness across the anterior part of the chest. He had no fever. He tried to return to work after a fortnight, but was unable to do so because of aggravation of the pain in his chest, and dyspnea on slight effort and on talking to customers. Examination by many physicians revealed no cause for his symptoms until nine months after the accident, when an electrocardiogram was taken and showed bundle branch block. Physical examination was essentially negative, except for some sclerosis of the radial and temporal arteries. The eye grounds were normal. The heart was not enlarged. The heart sounds were of good quality, and there were no murmurs. The blood pressure was 110/60.

This type of cardiac damage, caused by direct blows to the chest wall, may be due to contusion of the heart, with hemorrhage into the myo-

cardium, or to injury of one of the coronary arteries. Violent jars to the body may have a similar effect. The heart is suspended from the aorta, and hangs free in the mediastinum. A sudden, forcible fall may induce a vigorous pendulum-like movement of the heart, and traumatize it severely. I can cite several cases that seem to fall into this category.

CASE 2.—A hotel manager, aged 45, had been under my care since 1932. He had never had any serious illness, nor any symptoms or signs referable to any abnormality of the heart. While on his vacation in the fall of 1939 he played baseball, and, when batting, missed the ball, stumbled, and fell on his buttocks. At first he thought he was unhurt, but a few minutes later began to experience substernal oppression and difficulty in breathing, and soon broke out in a cold sweat. The pain persisted for several hours, until he received an injection of morphine. Precordial oppression lasted all night. I saw him two days later. The heart was somewhat enlarged; the heart sounds were very faint; and the rate was rapid. The blood pressure was 84, systolic. The following day a pericardial friction rub was heard. Fever persisted for a week. The electrocardiogram revealed the classical picture of infarction of the posterior aspect of the left ventricle. Two weeks after the onset of symptoms, right-sided hemiplegia and aphasia occurred suddenly. The patient has continued to have a very poor cardiac reserve, with a persistent hemiplegia and aphasia.

A similar case has been reported by Kienle.<sup>8</sup>

#### EFFORT

The interpretation of the mechanism of cardiac infarction which occurs during or after effort is of the greatest practical significance. Those who have held that effort is not directly concerned with the induction of cardiac infarction have relied largely on statistical evidence. They have pointed out the fact that, in many cases, cardiac infarction occurs while the patient is at rest or asleep, and that, when effort and cardiac infarction occur simultaneously, the relationship is coincidental, not causal. To me this is very specious reasoning. We might as well say that, because only rarely can we demonstrate a direct connection between local irritation and cancer, chimney sweeps' cancer of the scrotum has nothing to do with their occupation. As Bean recently pointed out, the fact that most motor accidents do not occur at speeds of 70 miles an hour does not prove that such speeds may not be concerned in some motor accidents.

With the growing accumulation of cases in which there seems to be such a direct connection between effort and the onset of cardiac symptoms, and with our clearer understanding of the physiologic mechanisms, particularly that of cardiac infarction without coronary thrombosis, we must accept this relationship as a very definite one.<sup>9</sup> Indeed, it is my conviction that the more carefully we delve into the history of patients who have had cardiac infarction, the more often will we find definite precipitating causes. Clinicians of a previous generation recognized that effort might precipitate a fatal attack in patients with coronary

disease. Thus Osler<sup>10</sup> writes: "Hurrying to catch a train has often been the exciting cause of a fatal attack in the subjects of angina. The muscular and mental excitement of coitus is particularly dangerous, and has in many instances caused death."

I propose to present some cases that exhibit this relationship.

In 1906, James Mackenzie recorded a classical example.<sup>11</sup>

A builder, aged 48, for some months had had slight substernal pain on walking uphill. One day while overseeing his men he felt cold. To warm up he helped them dig for fifteen minutes, and then ran up and down the stairs of some partly built houses. On his way home he experienced substernal pain of increasing severity. The pain became very intense, radiated down the left arm, and lasted hours, until opium was given. It recurred the following morning, and was accompanied by a drenching sweat. After three weeks' rest he made a good recovery.

The following cases are from my files.

CASE 3.—A man, aged 62, a tailor, had always been well and had had no symptoms referable to his heart until Oct. 6, 1940, when he helped his son push a stalled automobile. While pushing the car he broke out into a cold sweat, became dizzy, and experienced severe squeezing pain across the mid-chest which lasted twenty minutes. He had to sit down immediately, and rested the remainder of the day. That night he was awakened by a similar pain which lasted an hour and a half. The next day, however, he returned to work, and, from time to time, experienced mild substernal pain for which he would rest for a short time. On October 11 he again had a nocturnal attack which lasted two hours, but he returned to work the next day. On this day, for the first time, he noted substernal pain on walking two blocks, compelling him to rest. This symptom of angina on effort persisted until I saw him on October 26. Physical examination revealed few abnormalities. The heart was not enlarged. The first heart sound was of good quality. The aortic second sound was accentuated. There was a systolic murmur at the apex. The blood pressure was 150/80. The electrocardiogram showed low voltage and abnormal R-T segments in Leads I, II, and IV.

This case illustrates a number of significant features which are frequently encountered. Anginal symptoms came on suddenly, and for the first time, during severe effort. This was followed twelve hours and, again, five days later by prolonged, spontaneous attacks of anginal pain. After the second spontaneous attack, classical angina on effort set in and continued. Throughout this whole period, during which cardiac infarction occurred, the patient continued up and about and at work.

CASE 4.—A truck driver, aged 37, had been perfectly well and had worked hard without any symptoms until Nov. 9, 1940. He was loading some heavy cases on his truck; four cases had already been loaded, and he was working on the fifth case, assisted by three other men. This case weighed about 1,100 lbs. He used a case hook and lifted it with two hands, using all his strength to get it on a hand truck. While engaged in this maneuver, he experienced a pressing pain across the anterior part of the chest. Although the pain continued, he helped finish loading the case onto his truck and helped with one more case. However, he did not exert

rate was 100; and the electrocardiogram was unchanged. He was admitted to the hospital, where he ran a typical course of cardiac infarction. He made a good recovery and two years later was well and asymptomatic.

In this case it is a question whether the typhoid injection induced the cardiac infarction through the nonspecific effect of the chill and fever, or whether the typhoid injections two years previously had sensitized him, so that it was in the nature of an allergic reaction.

Cardiac death after intravenous typhoid injection has been reported.<sup>24</sup> A man who had had no symptoms referable to the heart received typhoid vaccine for a toxic erythema. Three hours after the injection, at the height of the febrile reaction, the patient collapsed and died within an hour. At autopsy an old healed infarct was found in the anterior wall of the left ventricle, and a fresh thrombus, without a fresh infarct, was discovered proximal to the old lesion.

Cases have been described of persons who developed urticaria and anginal pain, with definite, but transient, electrocardiographic changes, after the ingestion of acetylsalicylic acid.<sup>25</sup> Attacks could be produced at will by taking the drug. These patients had preexisting coronary disease. Shookoff and Lieberman<sup>26</sup> observed a man, aged 63, with asthma and hay fever due to ragweed. One August he developed severe, frequent, anginal attacks at rest, in the absence of hay fever and asthma. The attacks were controlled only when the patient was placed in a room, the air of which had been freed of pollen by filters.

CASE 9.—A man, aged 53, had had hay fever for three years. For six months he had been receiving injections, in large doses, for the treatment of hay fever. Invariably, two or three hours after each injection, he experienced substernal cramps which lasted one to two hours. The dosage of the injections was reduced, and, although the attacks persisted, they were of less intensity. He complained of similar pain when he lifted heavy things, when he climbed stairs, and on excitement. General physical examination was negative. Fluoroscopic examination revealed a heart of normal size and configuration. The heart sounds were of good quality. There were no murmurs. The blood pressure was 140/90. The electrocardiogram was normal.

The evidence clearly suggests that in certain instances allergic reactions may give rise to attacks of angina pectoris or of cardiac infarction.

#### COLD

It has been known for years<sup>27</sup> that drinking ice water may cause an immediate inversion of the T waves in Leads II and III. Luten<sup>28</sup> described two cases of cardiac infarction which occurred immediately after drinking ice water. In such instances the diaphragmatic portion of the heart is chilled directly by the ice water in the stomach. Chilling of the body commonly induces anginal seizures. It is commonplace for a patient with coronary artery disease to experience an anginal seizure as

soon as he steps out of his house on a cold winter day, or on going to bed between cold sheets. The mechanism here is probably a reflex one. Moderate exertion in cold weather often immediately precedes cardiac infarction. In these cases two factors are simultaneously operative, namely, reflex coronary spasm and effort. A number of statistical studies have shown that cardiac infarction occurs more frequently during the cold than during the warm months of the year.<sup>20</sup> I have had a number of patients whose symptoms of cardiac infarction commenced while they were trudging through deep snow on a cold winter day. Every winter I see a number of patients who experienced the initial symptoms of cardiac infarction while shoveling snow.

On March 2, 1941, the day after a severe snow storm, the *New York Times* reported eight deaths caused by the storm in New Jersey. Three men died of heart attacks while shoveling snow. One man, aged 73, died while fighting his way through the snow, and another man died of a heart attack while helping a stalled motorist out of a drift.

#### INFECTIOUS DISEASE

I have observed not a few patients who had an intercurrent infection which appeared to precipitate coronary thrombosis or cardiac infarction. Often these infections are relatively mild, i.e., so-called grippe, or mild bronchitis. Huehard<sup>30</sup> wrote that deaths from angina pectoris are very frequent during grippe epidemics.

CASE 10.—A man, aged 57, had had a peptic ulcer for thirteen years, with intermittent symptoms. The ulcer symptoms had been active during the second half of 1939. During the same period he complained of burning pain in the left upper extremity. Several weeks before I saw him he caught cold, and complained of a cough, chilliness, and a mild heaviness in the upper mid-chest. He was in bed for two days. He left the bed on the third day and went to his store. He felt the same heaviness in the upper mid-chest, which soon turned into a pain severe enough to necessitate a hypodermic injection. He returned home and was in bed for six weeks. He was examined seven weeks after the onset. General examination was negative. Fluoroscopic examination revealed a heart of normal size and configuration. The heart sounds were dull. There were no murmurs. The electrocardiogram showed left axis deviation and a diphasic T wave in Lead IV.

#### OPERATION AND HEMORRHAGE

It is unnecessary to dwell on surgical operations as an immediate cause of cardiac infarction. Today this sequence is recognized by most cardiologists.<sup>31</sup> Shock or hemorrhage may reduce coronary flow to a point at which irreversible myocardial damage occurs. When the cardiac infarction occurs several days after the operation, alterations in coagulability of the blood may play a role. I have seen a number of patients whose cardiac infarction followed extraction of a tooth.

CASE 11.—A man, aged 55, was first seen in April, 1938. He had had an enlarged heart for years, but no cardiac symptoms until a year previously, when he began



experiencing typical angina pectoris, at first only on exertion, but subsequently, spontaneously at night. General physical examination was negative except for moderate pallor. Fluoroscopic examination revealed much enlargement of the left ventricle and moderate enlargement of the left auricle. The secondary branches of the pulmonary arteries were dilated. The first heart sound was of good quality; the second sound was reduplicated. At the apex there was a loud, musical, systolic murmur which was transmitted to the axilla. The blood pressure was 100/60. The electrocardiogram showed rather low T waves in the three limb leads, and a deep Q wave, with an upright T wave, in Lead IV. He was seen again in January, 1939. He had become very pale; the hemoglobin was 38 per cent. His stool gave a positive guaiac test. General physical examination was still negative. Repeated roentgenograms of the colon were negative, and, under iron therapy, the hemoglobin rose to 70 per cent. In June, 1939, he had a severe intestinal hemorrhage, with collapse. A few hours after this he was seized with severe substernal pain which lasted hours and required morphine for relief. The electrocardiogram revealed the typical pattern of posterior infarction. The heart sounds were poor, and he was febrile for ten days. When he recovered from his cardiac infarction, he had another roentgenogram of his colon, and a carcinoma of the ascending colon was finally discovered. He was operated on and made a good recovery.

A variety of other factors may precipitate cardiac infarction. Probably the most common is the eating of too large a meal. Cardiac infarction occurs frequently after a banquet, or after the evening meal, particularly when the patient has been very hungry because he has not eaten all day. Grollman<sup>32</sup> has shown that the cardiac output may increase by as much as 2 liters a minute after a heavy meal, and he suggests that this increased load on a heart with diseased coronary arteries may explain the occurrence of death after a large meal.

Cardiac infarction as a result of insulin shock and hypoglycemia has been described repeatedly.

Severe electric shock may induce angina pectoris or cardiac infarction.<sup>33</sup>

High altitudes, such as those attained during airplane flights, induce anoxemia which may be sufficient to cause coronary insufficiency or myocardial infarction in persons with diseased coronary arteries. Benson<sup>34</sup> described the case of a pilot who developed symptoms of cardiac infarction while flying over a mountain pass in California. At autopsy, extensive atheroma of the descending branch of the left coronary artery was found, but there was no myocardial infarction.

It is probable that excessive heat or humidity may at times induce cardiac infarction.<sup>35</sup> One of my patients had his attack in a Turkish bath.

CASE 12.—A man, aged 55, for three years had complained of pain in the calves on walking three blocks, compelling him to rest. He last obtained life insurance one year earlier. He visited a Turkish bath and remained there for two hours. As he was about to leave, he suddenly became dizzy, broke out into a sweat, and experienced substernal pressure which lasted an hour. While dressing, the pain recurred. He was then taken to a hospital, where he remained for six weeks.

Examination thirteen weeks after the onset revealed some enlargement of the left ventricle and left auricle. The first heart sound was obscured by a loud systolic murmur at the apex, which was transmitted to the axilla. The blood pressure was 110/80. The electrocardiogram showed the typical pattern of posterior infarction of the left ventricle.

#### CONCLUSION

I have cited case histories to illustrate the fact that the onset of cardiac infarction is often preceded by specific events that seem to be directly responsible. To the popular mind this is a common and natural sequence of events. Physicians, in spite of the fact that they may, on theoretical grounds, deny that there is any causal relationship between external factors and the development of cardiac infarction, take great pains to warn their patients with coronary artery disease against physical exertion, overeating, and sexual excitement.

Present knowledge of the physiology and pathology of the coronary circulation suggests probable mechanisms that may initiate cardiac infarction. Fundamentally, there is an upset of the balance between the nutritive needs of the heart muscle and the adequacy of the coronary blood flow, and this is sufficient to cause myocardial necrosis. Such coronary insufficiency arises most commonly because the narrowed channels of the diseased coronary arteries do not permit the passage of enough blood to satisfy the needs of the heart muscle when there are sudden calls on it for greater work; the flow of blood is decreased because of reflex narrowing of the damaged coronary arterial bed, or by hemorrhage into the coronary arterial wall, causing partial or complete occlusion of one of the coronary vessels.

The most common external factors which precipitate cardiac infarction are effort, emotion, cold, and overeating. These factors cannot cause cardiac infarction in the presence of normal coronary arteries. Just as an unhealthy tree may stand for years until blown down by a violent wind storm, so a heart, with sclerosed coronary arteries, may function for years until a sudden strain overtakes its weakened structure and leads to cessation of heart action, or impairment of its structure and function, with progressive heart muscle damage.

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# HEART DISEASE AND PUBLIC HEALTH

## CURRENT TRENDS AND PROSPECTS

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AS I am to discuss heart disease and public health, it will avoid misunderstanding if at the outset I attempt to define what we mean by public health. It is that branch of medicine which concerns itself with the prevention and control of disease from the point of view of the community as a whole. In contrast with the practicing physician, the health officer has the people of the city, county, state, or nation as his patients, and he utilizes the resources of the community in his effort. We all know that, under modern conditions, the individual patient and the individual doctor are often helpless in combatting the spread of infection, as, for example, in controlling yellow fever, typhoid fever, or malaria. It takes the resources of the state to do that. Even in relation to such diseases as tuberculosis and syphilis, it has become a well-established principle, learned through sad experience, that not only prevention, but treatment, is properly a public health function. The individual patient, in many instances, is unable to provide himself with the care which he needs, and the community is to that extent endangered. The public interest, therefore, demands that the necessary treatment be given, even if at public expense. In all this, there is no real conflict between the public health officer and the individual practicing physician. There are broad areas of mutual interest. The wise health officer will attempt to make all practicing physicians his associates, and all good doctors will look to their health officer for guidance and support in helping them with their patients. These general principles are gradually being evolved, although they have not yet been completely crystallized. The functions of the health officer, on the one hand, and of the practicing physician, on the other, are being worked out in the light of experience and of changing conditions, and the public interest, in the last analysis, determines their mutual responsibilities.

What are the most important problems in heart disease, and what is or should be the relationship of the public health officer to them? Heart disease is the outstanding feature of the medical picture, and will be increasingly so in the future. Clearly, the health officer cannot ignore a field so wide in extent and affecting the public health so vitally. Essen-

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tially, his problems in this field are the same as those of the practicing physician, although his approach and functions are necessarily different. As I have already indicated, the health officer must concern himself with those phases of heart disease in which large-scale prevention or measures of control are attainable. The well-recognized public health procedures are clearly applicable to the control of rheumatic fever and syphilis. The control of premature hypertensive and arteriosclerotic heart disease has to date received scarcely any attention from health officers. Imperceptibly shading off from the last category is the numerically most important group, which comprises cardiac disease in old people. To a greater or lesser degree, the health officer, as we shall see, can function to advantage in all of these four phases.

Rheumatic fever is today one of the foremost health problems of childhood. Between the ages of 5 and 9, deaths from it are outnumbered only by those from the four principal communicable diseases of childhood, as a group, and by pneumonia.\* At the ages of 10 to 14, it is the leading cause of death. Between the ages of 15 and 25, it is second only to tuberculosis. Although it is true that the mortality from rheumatic fever has declined, the rate of fall is less than that from other diseases, so that the proportion of deaths from rheumatic fever to the total number of deaths among persons under the age of 25 has increased.

By its very nature, rheumatic fever is a disease in every phase of which the health officer can be of great help, but he has done comparatively little. He may actively participate in a case-finding program. He can take over or amplify facilities for the treatment and care of children with the disease. Practically nowhere are these facilities commensurate with the needs. His laboratory can function in research in rheumatic fever, the cause of which has thus far eluded scientific investigation, and his records may help to unravel the complex epidemiology of the disease. He can provide convalescent and sanatorium care in suitable types of institutions. In certain parts of the country he can make use of facilities built for other purposes, but which are not fully used, particularly the tuberculosis sanatoriums. Furthermore, since non-specific factors seem to be responsible for most of the decline in rheumatic fever, public health officials can actively promote improvement in certain matters which come under their aegis or in which they have some influence, as, for example, in housing and in popular education in health and nutrition.

In the control of syphilis, the health officer has already contributed a great deal. In fact, the progress that has been made reflects the degree to which health officers have been willing and able to take responsibility, not only in finding cases but also in treatment. In the Scandinavian countries, where syphilis has been largely controlled, it has

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\*Since this paper was written, mortality from pneumonia has fallen below that for rheumatic fever.

been the public health service which has carried the brunt of the work. If in our country some progress in this direction has been made, there is no denying the fact that in the present national emergency, with huge numbers of young men concentrated in camps and in defense industries, and with no correspondingly increased facilities for handling the case load, we may lose the gains of the last ten years. The task of the health officer is manyfold—finding the victims of the disease, and providing adequate facilities for treatment and seeing that they are used. He needs a broad concept of his job and resourcefulness in dealing with it.

The most difficult aspect of the problem in heart disease, both for medicine and for public health, is constituted by the relatively large numbers of persons in the prime of life who fall prey to early and sometimes preventable heart and coronary artery diseases of other etiologic types. They affect men chiefly. The root of much of this problem is probably related to the process of aging of the human organism, the study of which has been scarcely begun. Fortunately, there is increasing awareness of the necessity for research on the fundamental problems involved, and a number of medical men and other scientists and public agencies are already engaging in this work. Notable is the work being done in one public institution, the Research Unit of New York City's Hospital for Chronic Diseases, and in several other places. But a greater part of our public medical resources can and should be devoted to this field.

Apart from this, however—and the wide difference between the death rate of the two sexes is, in my judgment, a good indication—a large number of early deaths from heart disease can be avoided or postponed. Many are probably due to faulty living habits with respect to the routine of daily life, or to lack of attention to infections. Intensive research and popular health education, both of which are important functions of modern public health organizations, can do a great deal in this regard.

For one thing, the health officer can help in the early detection of incipient heart disease by popularizing the periodic medical examination. In this matter a more receptive attitude on the part of the medical profession generally is much to be desired. It is admittedly true that symptoms of early heart disease are often hard, sometimes impossible, to detect, but too many patients receive little or no medical supervision until long after the disease has progressed. It may not be too early for the two professions to consider the desirability of providing public clinics for the periodic medical examination of certain groups of the population that cannot themselves afford such service.

The public health officer should consider in what ways, efficient and economical, he can utilize available medical resources in cases of early heart disease, or in acute attacks of chronic disease. For example, do we not all know of working men and women with cardiac disease who

would benefit from relatively short periods of sanatorium care, where prescribed rest and other measures would be carried out under suitable conditions, and where re-education of the patient in his way of life could be carried out better than in the atmosphere of worry and strain of the home and work place? In a few places, the overbuilt sanatorium facilities for tuberculosis, or other hospitals now unutilized, could be devoted to this purpose.

The health officer can make increasing use of the visiting nurse services under his supervision for chronic cardiac disease and, when such services are lacking, can develop or amplify them. Visiting nurses now operating very widely all over the country are of value not merely in actual bedside care, but in the broader fields of psychological adjustment of the patient or his family, and in interpreting the doctor's instructions to them. These phases are often neglected because they take more time than the busy physician can give them. But they can be handled well by visiting nurses, particularly if nurses are given special training.

Old people with cardiovascular disease present a somewhat different set of problems which are much more difficult in character and limited in scope. The chief needs are for additional clinic facilities, for more home care, and for institutional care of the semihospital type. The numbers of aged cardiac patients are already so great and so rapidly increasing that there is urgent need for a long range program for their care. The very nature of the situation is such that a major part of the financial burden must be borne by public funds. Public health officers must recognize their responsibility here and seek the help and guidance of the whole medical profession in developing programs that are consonant with the welfare of the patients, the public, and the doctors. We cannot safely add to the burdens of voluntary hospital clinics if they are to continue to do good work. A larger number of public clinics, run by full-time men, is the only desirable solution for impoverished ambulant patients. When such patients are confined at home, public medical service may be necessary, but the work of physicians may be lightened and rendered more efficient by the proper use of visiting nurses and, in selected cases, of medical social workers. Increasing numbers may best be handled in institutions, but these cannot and need not be elaborate and costly hospitals.

Heart disease, then, presents many different tasks, responsibilities, and opportunities for public health officers. But before any large-scale advance can be made, both they and the medical profession as a whole must accept the view that heart disease is a proper field of work for the health officer. They need also to agree on the respective roles of the private and public physician.

In this respect, the problem of heart disease reminds one of the situation which prevailed in tuberculosis about thirty years ago. At that time health officers were just beginning to recognize that the problem



of the tuberculous patients was largely one for them to solve. There was considerable hesitation in entering the field, and uncertainty in developing the necessary technique and procedures. They lacked diagnostic classifications and standards, staffs trained in the special treatment of the disease, and sufficient diagnostic and sanatorium facilities for the care of patients.

What a change thirty years has brought about, thanks to the increasingly better understanding of the basic factors of the situation by both practicing physicians and the growing profession of health officers. Once it was realized that a disease so widespread, yet everywhere so concentrated among poor people, was the province of the public authorities, constructive steps, one after another, were taken by health officers and physicians in developing new procedures, with the result that, within a single generation, prodigious advances were made, not only in cutting down the ravages of the disease, and in protecting persons against it, but also in developing an understanding of the nature of the disease itself.

I am bold enough today to stress this analogy with reference to heart disease. I appreciate, of course, inherent and fundamental differences between the one disease which stems from an invasion of the body by a bacillus, and the other disease or group of diseases, the bulk of which represents sequelae of many factors, both exogenous and endogenous in nature, in the aging patient. Prevention of tuberculosis did not prove a hard nut to crack once the nature of the problem was understood and properly organized efforts were brought to bear. Prevention of heart disease will be a very different proposition because so large a part of it is the end result of accumulated insults incidental to the functioning of the body. On the other hand, there are enough phases of heart disease in which prevention is possible to excite the health officer with the real job he can do in this field.

But my major interest is the idea that the field of heart disease is fundamentally one in which the health officer can function and bear a major responsibility. There is every reason why the organized official and voluntary public health agencies should participate in the work to be done. Health officers have a tremendous contribution to make in supplementing and strengthening the efforts of the medical profession and in developing appropriate administrative procedures for the practical care of patients. For this disease, the most common in adult life, involves such long periods of disability that the medical costs are far beyond the resources of most of its victims. The very economies of the situation make it impossible for the ordinary relationships of physician and private patient to be fully effective. Thus far this situation has been met by the establishment of free or low-cost outpatient clinics in public and private hospitals, in which much of the service of the physician is rendered without compensation. Patients either cannot be

seen sufficiently often or are treated too superficially because of the crowded conditions of most of the clinics. This situation will get worse, rather than better. Obviously, we must think in terms of modifying our present types of organization and medical care for these people.

Leaders in medicine and public health must face frankly a situation as patent as this, and take the necessary steps for integrating the care of those suffering from heart disease into a general scheme, in which the proper share is borne by public funds, under the administration of the health officer, just as has been done in the case of tuberculosis. I have no illusions that this scheme can be developed overnight. The tuberculosis problem, which was simpler, took decades to get under way toward solution. But the important and first step is the acceptance by physicians and health officers of the concept that heart disease is a suitable field for similar exploitation. Then, in good will, all interested parties can get together in planning their respective parts of the job, on ways of effective cooperation, and on the sequence of steps which would be most likely to assure progress and win the support of the community.

# THE VALUE OF COMBINED MEASUREMENTS OF THE VENOUS PRESSURE AND ARM-TO-TONGUE AND ARM-TO-LUNG CIRCULATION TIMES IN THE STUDY OF HEART FAILURE

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MUCH has been written on measurements of the venous pressure and circulation time of the blood in connection with various cardiovascular diseases. The value of such measurements in the diagnosis and continued observation in cases of heart failure has been especially emphasized. However, most of the clinical studies on heart failure have been concerned with one or another of these tests as an isolated procedure. Comparatively little information has been published which would indicate the importance, at times, of estimating the venous pressure and measuring the circulation time more or less simultaneously. It has been our purpose in this investigation to endeavor to appraise the value of these measurements when they are used in combination.

## TECHNIQUE

The apparatus (Fig. 1) we used for combined measurements of the venous pressure and circulation times consists of a three-way stopcock to the center adaptor of which is connected, by means of rubber tubing, a calibrated glass tube of 4 mm. bore. This measuring tube is filled through the stopcock with physiologic salt solution by means of a 5 c.c. syringe. This syringe is then filled with 5 c.c. of a 20 per cent calcium gluconate\* solution (or 10 per cent magnesium sulfate solution) and is attached to the stopcock. A 1.5 inch, 19 gauge needle is affixed to the other end of the stopcock. A mixture of 5 minims of ether and 5 or more minims of physiologic salt solution is placed in a 2 c.c. syringe and kept at hand.

The patient is required to rest in bed for at least fifteen minutes before the measurements are made. He is instructed in those parts of the procedure which will require his cooperation. He is requested to try to breathe regularly and naturally and to refrain from talking except as specifically directed. At the time of the measurements, the patient should be supine. The arm selected for venipuncture is abducted through an angle of about 45 degrees, and is in such a position that the antecubital veins are at, or slightly below, the plane of the right atrium. The location of this plane is indicated on the side of the patient's chest by placing a mark 10 cm. from the plane of his back. This mark serves as the zero level for measurement of the venous pressure. It has been demonstrated<sup>1</sup> that this method

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\*Calcium gluconate was supplied as ampoules of 20 per cent Neocalglucon by the Sandoz Company.

of allocating the plane of the right atrium is more exact than older methods which took their measurements from the front of the chest. Occasionally, when the patient is too dyspneic, because of pulmonary congestion, to lie flat in bed, the venous pressure and circulation times must be estimated with him in a sitting position. When this is the case, the plane of the right atrium is considered to be at the level of the fourth rib. However, it has been our experience that the venous pressure cannot be measured so accurately under these conditions.

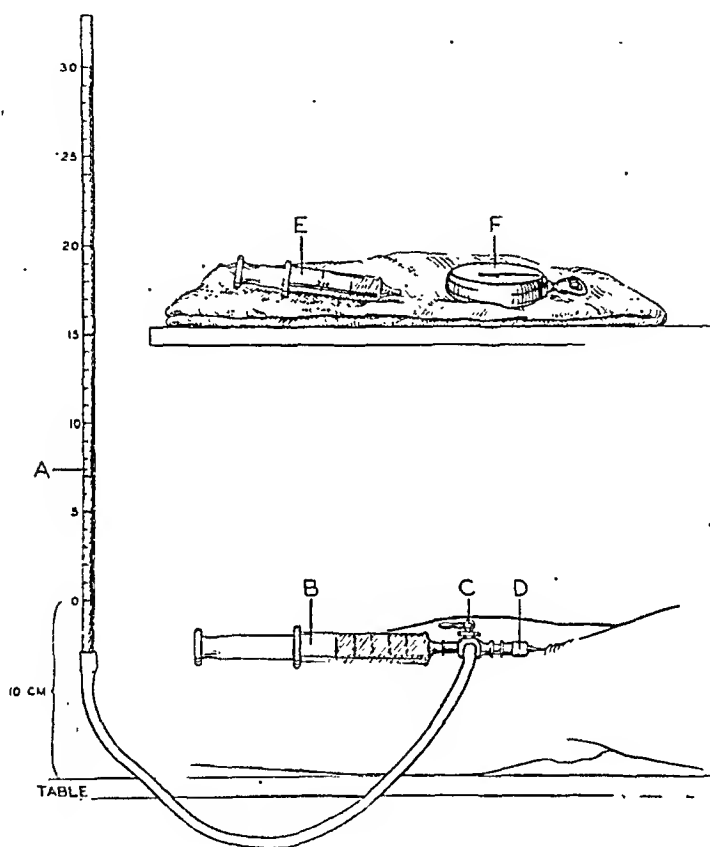


Fig. 1.—Apparatus for measurement of circulation times and venous pressure. *A*, Calibrated tube; *B*, 5 c.c. syringe; *C*, three-way stopcock; *D*, 19 gauge needle; *E*, 2 c.c. syringe; *F*, stop watch. (From *The Practitioner's Library*, Supplement Volume, New York, 1940, D. Appleton-Century Co., Inc.)

The needle of the apparatus is introduced into one of the antecubital veins, according to the usual technique for venipuncture. When the tourniquet is removed from the patient's arm, ten to fifteen seconds are allowed to pass in order to permit the restoration of venous flow that has been retarded by the tourniquet. Then the calcium gluconate or magnesium sulfate is injected as rapidly as possible. The interval from the beginning of this injection until the patient says "Hot," at the moment of perception of a hot sensation in his throat and tongue, is measured with a stop watch, and represents the arm-to-tongue circulation time. It ranges in normal persons from nine to sixteen seconds.

As soon as the first injection is completed, the lever of the stopcock is turned so that salt solution will begin to enter the vein from the glass measuring tube. Next, the 5 c.c. syringe is replaced at the stopcock by the smaller syringe contain-

ing the ether-saline mixture. Meanwhile, the zero point of the glass measuring tube is placed at the mark on the patient's chest which designates the plane of the right atrium. The column of saline in the tube will continue to fall, fluctuating slightly with respiration, and finally comes to rest at a height which indicates the venous pressure in terms of millimeters of saline. The patient's abdomen is then compressed at the right upper quadrant for thirty to sixty seconds, in order to record the effect of this procedure upon the height of the venous pressure.<sup>2</sup> Compression of the abdomen should be firm, but should not interfere with the regularity or depth of the patient's breathing. Normally, the venous pressure varies from 50 to 150 mm. of saline, and, when the abdomen is compressed, there is no rise or a rise of less than 10 mm.

After the venous pressure has been measured, the patient is warned that the next part of the procedure will require his active cooperation. The lever of the stopcock is returned to its original position, and the ether-saline mixture is injected as rapidly as possible into the vein. The interval from the beginning of this injection until the patient perceives the odor of ether, and says "Now," is measured by means of a stop watch, and represents the arm-to-lung circulation time. Occasionally the operator will smell the ether on the patient's breath before the patient speaks. In this event the end point of the measurement is the moment at which the operator detects the odor. Normally, the arm-to-lung circulation time ranges from 3.5 to eight seconds. It is now possible to compute the lung-to-tongue circulation time by ascertaining the difference between the two circulation times already estimated. The lung-to-tongue circulation time normally varies between five and twelve seconds.

#### HEART FAILURE

The measurements were recorded, according to the technique described above, in 100 consecutive cases of congestive heart failure of varying severity and under varying conditions of treatment. The cases comprised a number of different etiological types of heart disease (Table I). The number of times the measurements were performed in each case ranged from one to eight, depending upon whether or not it was desirable or feasible to repeat them as a part of the observation of the patient's clinical course. A total of 185 measurements were made in the 100 cases (Table II).

The patient with heart disease who develops symptoms and signs of general heart failure always shows abnormalities in these measurements. Thus, the venous pressure usually is considerably above 150 mm. of saline, and rises quickly and significantly when the right upper quadrant of the abdomen is compressed. The arm-to-tongue circulation time is prolonged beyond sixteen seconds, and the arm-to-lung circulation time, as measured with ether, is more than nine seconds. Practically all of the patients in this series had measurements characteristic of general heart failure. Thus, 148 measurements which were made in eighty-nine of the 100 cases indicated the presence of general heart failure. The highest venous pressure obtained initially in this series of patients with heart failure was 335 mm. of saline, with a rise to 390 mm. when the right upper quadrant of the abdomen was compressed. The longest

arm-to-tongue circulation time, as measured with calcium gluconate, was seventy-five seconds. The longest arm-to-lung time, as measured with ether, was thirty-four seconds.

TABLE I  
ETIOLOGICAL CLASSIFICATION OF CASES OF HEART FAILURE

| DIAGNOSIS                   | NO. OF CASES |
|-----------------------------|--------------|
| Rheumatic heart disease     | 13           |
| Hypertensive heart disease  | 57           |
| Syphilitic heart disease    | 14           |
| Coronary arteriosclerosis   | 8            |
| Hyperthyroid heart disease  | 3            |
| Beriberi heart disease      | 2            |
| Heart disease due to anemia | 1            |
| Undetermined etiology       | 2            |
| Total                       | 100          |

In cases in which the heart failure responds to treatment, there is a tendency for these values to return more or less promptly to normal. Usually, the arm-to-lung circulation time is the first to be restored. Even when this time has reached a normal value and the initial venous pressure measurement is no longer above 150 mm. of saline, the tendency of the venous pressure to rise significantly when the abdomen is compressed may persist for a variable length of time. In thirty-three of the cases of heart failure the arm-to-lung circulation time was normal, but measurement of the venous pressure indicated the existence of right ventricular failure, either by an initially high reading or by a significant rise when the abdomen was compressed. Three of the thirty-three patients had hyperthyroid heart disease.

The arm-to-tongue circulation time sometimes remains prolonged for a considerable period after the other values have returned to normal. This is particularly true in cases of hypertensive, arteriosclerotic, and syphilitic heart disease. There were thirteen cases in our series in which this was observed. In an occasional case of this type the arm-to-tongue circulation time apparently never reaches a normal value, indicating presumably that some degree of left ventricular failure remains.

In some cases of heart failure, the clinical manifestations are indicative only of failure of the left ventricle during the entire time that the patient is under observation. Of course, after a variable length of time, manifestations of right ventricular failure may ensue. When there is failure of the left ventricle only, the venous pressure and arm-to-lung circulation time remain relatively normal, but the arm-to-tongue circulation time is prolonged. In seven of the 100 cases in our series the clinical manifestations were those of isolated left ventricular failure, and the circulation measurements were in keeping with this diagnosis. When the venous pressure or circulation time is measured for the first time

TABLE II

RESULTS OF MEASUREMENT OF VENOUS PRESSURE AND CIRCULATION TIMES IN 100 CASES OF HEART FAILURE

| CASE NO. | ETIOLOGY | DATE   | TREATMENT              | SIGNS OF HEART FAILURE                           | VENOUS PRESSURE          | RIGHT UPPER QUADRANT COMPRESSION | ARM-TO-TONGUE CIRCULATION TIME     | ARM-TO-LUNG CIRCULATION TIME          | LUNG-TO-TONGUE CIRCULATION TIME |
|----------|----------|--|------------------------|--|--------------------------|----------------------------------|------------------------------------|---------------------------------------|---------------------------------|
| 1        | 1        | 10/10/39<br>10/14/39<br>10/23/39<br>10/30/39 | U.<br>P.D.<br>D.<br>D. | E., T., P.<br>E., T., P.<br>E., P.<br>E., T., P. | 150<br>185<br>165<br>220 | 180<br>250<br>250<br>300         | C. 26.5<br>C. 48<br>M. 38<br>M. 65 | Et. 11<br>Et. 9<br>Et. 15<br>Et. 18   | 15.5<br>39<br>23<br>47          |
| 2        | 2        | 10/13/39<br>10/17/39<br>10/26/39             | U.<br>P.D.<br>D.       | E., P.<br>E.<br>O.                               | 250<br>130<br>110        | 300<br>150<br>110                | C. 22<br>C. 16<br>M. 14            | Et. 7<br>Et. 6<br>Et. 4.5             | 15<br>10<br>9.5                 |
| 3        | 2        | 4/26/39                                      | P.D.                   | T.   | 120                      | 130                              | C. 26                              | Et. 7                                 | 19                              |
| 4        | 2        | 7/13/40<br>7/17/40                           | U.<br>P.D.             | T., P.<br>O.                                     | 135<br>170               | 225<br>195                       | C. 45?<br>C. Blank                 | Et. 5.5<br>Et. 10                     | 39.5                            |
| 5        | 2        | 5/ 2/39                                      | D.                     | E., T., P.                                       | 190                      | 280                              | C. 26                              | Et. 10                                | 16                              |
| 6        | 1        | 4/28/39<br>5/ 3/39<br>5/ 8/39                | U.<br>D.<br>D.         | EE., T., P.<br>E., T., P.<br>E., T., P.          | 320<br>270<br>220        | 360<br>300<br>250                | C. 55<br>C. 47<br>C. 32            | Et. 22<br>Et. 15<br>Not done          | 33<br>32                        |
| 7        | 6        | 10/29/39                                     | U.                     | E., T., P.                                       | 165                      | 185                              | M. 22                              | Et. 6                                 | 16                              |
| 8        | 1        | 7/ 6/39<br><br>7/10/39                       | D.<br><br>D.           | T., P.<br><br>T., P.                             | 160<br><br>125           | 235<br><br>165                   | C. 18.5<br><br>C. 26               | Not done<br>Et. 6                     | <br>20                          |
| 9        | 2        | 11/27/39                                     | D.                     | T.   | 250                      | 300                              | M. 41                              | Et. 14                                | 27                              |
| 10       | 3        | 12/26/38<br>12/30/38<br>1/ 4/39<br>1/ 9/39   | U.<br>P.D.<br>D.<br>D. | EE., T., P.<br>T., P.<br>T., P.<br>T., P.        | 165<br>130<br>165<br>150 | 185<br>180<br>180                | C. 47<br>C. 35<br>C. 30<br>C. 37   | Et. 9.5<br>Et. 13<br>Et. 17<br>Et. 27 | 37.5<br>22<br>13<br>10          |
| 11       | 2        | 12/ 3/38<br>12/14/38                         | U.<br>D.               | T., P.<br>O.                                     | 250<br>110               | 300<br>120                       | C. 37.2<br>C. 27                   | Et. 13<br>Et. 12                      | 24.2<br>15                      |
| 12       | ?        | 11/23/39                                     | U.                     | EE., T., P.                                      | 335                      | 390                              | M. 30                              | Et. 9                                 | 21                              |
| 13       | 2        | 11/25/39                                     | D.                     | P.   | 220                      | 240                              | M. 19                              | Et. 11                                | 8                               |
| 14       | 3        | 1/ 3/39                                      | D.                     | T., P.   | 130                      | 150                              | M. 35                              | Not done                              |                                 |
| 15       | 1        | 6/ 8/39                                      | P.D.                   | EE., T., P.                                      | 215                      | 230                              | C. 37.5                            | Et. 12.5                              | 25                              |
| 16       | 1        | 6/10/39<br>6/25/39                           | U.<br>U.               | P.<br>P.   | 115<br>160               | 140<br>250                       | C. 12<br>C. 35                     | Et. 8<br>Et. 10                       | 4<br>25                         |
| 17       | 6        | 4/20/39                                      | U.                     | E., T., P.                                       | 220                      | 290                              | C. 26                              | Et. 21                                | 5                               |
| 18       | 2        | 1/ 3/40                                      | U.                     | EE., T., P.                                      | 320                      | 360                              | M. 55                              | Not done                              |                                 |
| 19       | 3        | 2/17/40                                      | D.                     | T., P.   | 110                      | 140                              | M. 26                              | Pa. 14                                | 12                              |
| 20       | 2        | 1/24/40                                      | D.                     | T., P.   | 140                      | 180                              | C. Blank                           | Et. 17                                |                                 |
| 21       | 2        | 12/ 4/39                                     | U.                     | E., T., P.                                       | 155                      | 175                              | M. 26                              | Et. 8.5                               | 17.5                            |
| 22       | 1        | 3/14/40                                      | D.                     | EE., T., P.                                      | 300                      | 350+                             | M. 36                              | Pa. 46<br>1.5 c.c.                    | -10                             |
| 23       | 5        | 2/ 9/40<br>2/15/40<br>2/27/40                | U.<br>D.<br>U.         | E., T.<br>T.<br>E., T., P.                       | 155<br>85<br>160         | 190<br>75<br>190                 | M. 13<br>M. 9<br>M. 10             | Pa. 6<br>Pa. 6<br>Pa. 6               | 7<br>3<br>4                     |
| 24       | 2        | 3/16/40                                      | D.                     | E.   | 110                      | 130                              | M. 25                              | Pa. 20<br>1 c.c.                      | 5                               |
| 25       | 2        | 3/20/40                                      | D.                     | E., P.   | 190                      | 210                              | M. 25                              | Pa. 25<br>1 c.c.                      | 0                               |
| 26       | 2        | 3/31/39                                      | U.                     | E., T., P.                                       | 300                      | 360                              | C. 26                              | Et. 9                                 | 17                              |

TABLE II--CONT'D

| CASE NO. | ETIOLOGY | DATE  | TREATMENT                      | SIGNS OF HEART FAILURE   | VE-NOUS PRES-SURE                   | RIGHT UPPER QUAD-RANT COM-PRES-SION  | ARM-TO-TONGUE CIRCULA-TION TIME              | ARM-TO-LUNG CIRCULA-TION TIME                    | LUNG-TO-TONGUE CIRCULA-TION TIME |
|----------|----------|---|--------------------------------|--|-------------------------------------|--------------------------------------|--|--|----------------------------------|
| 27       | 2        | 4/12/39<br>4/25/39                                      | P.D.<br>D.                     | T., P.<br>E., T.   | 230<br>185                          | 265<br>190                           | C. 23<br>C. 15.8                             | Et. 8.2<br>Et. 6.6                               | 14.8<br>9.2                      |
| 28       | 2        | 3/24/39<br>3/28/39                                      | U.<br>P.D.                     | T., P.<br>T., P.   | 240<br>125                          | 270<br>190                           | C. 46<br>C. 26                               | Et. 20<br>Et. 11                                 | 26<br>15                         |
| 29       | 2        | 3/30/39   | D.                             | EE., T., P.  | 270                                 | 350                                  | C. 39  | Et. 18   | 21                               |
| 30       | 2        | 3/ 9/39<br>3/14/39<br>3/18/39                           | U.<br>D.<br>D.                 | EE., T., P.<br>T., P.<br>P., D.  | 280<br>135<br>Not done              | 310<br>160                           | C. 24<br>C. 25.5<br>C. 25                    | Et. 8<br>Et. 7.5<br>Et. 14                       | 16<br>18<br>11                   |
| 31       | 2        | 3/13/39   | U.                             | E., P.   | 170                                 | 185                                  | C. 19  | Et. 10   | 9                                |
| 32       | 2        | 3/ 8/39<br>3/10/39<br>3/14/39                           | U.<br>P.D.<br>D.               | E., T., P.<br>E., T., P.<br>E., T., P.                                   | 260<br>270<br>110                   | 300<br>300<br>115                    | C. 44?<br>C. 60<br>C. 20                     | Et. 34<br>Et. 8<br>Et. 6                         | 10<br>52<br>14                   |
| 33       | 2        | 3/ 6/39<br><br>3/13/39                                  | U.<br><br>D.                   | E., T., P.<br><br>O.   | 140<br><br>75                       | 170<br><br>80                        | C. 60<br><br>C. 20                           | Not done<br>Et. 10                               | <br><br>10                       |
| 34       | 2        | 3/ 4/39<br>3/10/39                                      | P.D.<br>D.                     | E.<br>O.   | 150<br>90                           | 195<br>100                           | C. 18<br>C. 15                               | Et. 9<br>Et. 8                                   | 9<br>7                           |
| 35       | 1        | 2/ 7/39<br>2/17/39                                      | P.D.<br>D.                     | P.<br>P.   | 150<br>150                          | 180<br>165                           | C. 39<br>C. 45                               | Et. 9<br>Et. 11                                  | 30<br>34                         |
| 36       | 4        | 2/ 8/39<br>2/13/39<br>2/19/39<br>2/24/39                | U.<br>P.D.<br>D.<br>D.         | EE., T., P.<br>E., T., P.<br>T.<br>T.                                    | 230<br>120<br>60<br>120             | 300<br>165<br>70<br>150              | C. 20<br>C. 19<br>C. 21<br>C. 18             | Et. 10<br>Et. 6<br>Et. 6<br>Et. 8                | 10<br>13<br>15<br>10             |
| 37       | 3        | 2/13/39   | D.                             | E., P.   | 140                                 | 185                                  | C. 35  | Et. 10   | 25                               |
| 38       | 2        | 2/26/39<br><br>3/ 2/39                                  | U.<br><br>D.                   | E., T., P.<br><br>E., T., P.   | 260<br><br>125                      | Not done<br>150                      | C. Blank<br>C. 36                            | Et. 40?<br>Et. 5                                 | <br><br>31                       |
| 39       | 2        | 2/ 4/39<br>2/ 8/39<br>2/12/39                           | D.<br>D.<br>D.                 | E., T., P.<br>E., T., P.<br>E., T., P.                                   | 270<br>230<br>190                   | 310<br>260<br>220                    | C. 75<br>C. 22<br>C. 40                      | Et. 20<br>Et. 11<br>Not done                     | 55<br>11<br><br>                 |
| 40       | 2        | 2/ 2/39<br>2/ 6/39<br>2/11/39<br><br>2/25/39<br>3/ 4/39 | U.<br>D.<br>D.<br><br>D.<br>D. | EE., T., P.<br>EE., T., P.<br>E., T., P.<br><br>E., T., P.<br>E., T., P. | 275<br>260<br>230<br><br>315<br>280 | 310<br>310<br>300<br><br>335+<br>320 | C. 45<br>C. ?<br>C. 45<br><br>C. 35<br>C. 33 | Et. 20<br>Et. 19<br>Not done<br>Et. 11<br>Et. 22 | 25<br><br><br><br>24<br>11       |
| 41       | 3        | 12/ 1/38<br>12/ 4/38<br>12/ 9/38                        | U.<br>P.D.<br>D.               | E., P.<br>E., P.<br>P.   | 170<br>180<br>160                   | 195<br>190<br>170                    | C. Blank<br>C. Blank<br>C. 20                | Et. 25.8<br>Et. 24.8<br>Et. 16                   | <br><br><br>                     |
| 42       | 2        | 10/13/39  | U.                             | EE., T., P.  | 215                                 | 290                                  | C. Blank                                     | Et. 15   |                                  |
| 43       | 2        | 10/16/39<br>10/23/39<br>10/30/39                        | P.D.<br>D.<br>D.               | T., P.<br>O.<br>O.   | 160<br>165<br>50                    | 200<br>175<br>60                     | C. 24<br>M. 15<br>M. 10                      | Et. 10<br>Et. 10<br>Et. 5.5                      | 14<br>5<br>4.5                   |
| 44       | 2        | 7/24/39   | U.                             | EE., T., P.  | 225                                 | 375                                  | C. 34  | Et. 9  | 25                               |
| 45       | 2        | 10/29/39<br>11/ 2/39                                    | D.<br>D.                       | T., P.<br>P.   | 80<br>160                           | 120<br>185                           | M. 40<br>M. 50                               | Et. 26<br>Et. 12                                 | 14<br>38                         |
| 46       | 2        | 11/10/39<br><br>11/24/39                                | P.D.<br><br>D.                 | O.<br><br>O.   | 275<br><br>275                      | 300<br><br>350                       | Not done<br><br>M. 70                        | Not done<br><br>Et. 10                           | <br><br>60                       |



TABLE II—CONT'D

| CASE NO. | ETIOLOGY | DATE     | TREATMENT | SIGNS OF HEART FAILURE | VE-NOUS PRES-SURE | RIGHT UPPER QUAD-RANT COM-PRES-SION | ARM-TO-TONGUE CIRCULA-TION TIME | ARM-TO-LUNG CIRCULA-TION TIME | LUNG-TO-TONGUE CIRCULA-TION TIME |
|----------|----------|----------|-----------|------------------------|-------------------|-------------------------------------|---------------------------------|-------------------------------|----------------------------------|
| 47       | 3        | 12/ 8/39 | U.        | E., T., P.             | 225               | 285                                 | C. 42                           | Et. 19.5                      | 22.5                             |
|          |          | 12/12/39 | D.        | P.                     | 90                | 110                                 | C. 62                           | Et. 12                        | 50                               |
|          |          | 12/20/39 | D.        | P.                     | 65                | 75                                  | C. 26                           | Et. 10                        | 16                               |
|          |          | 12/26/39 | D.        | O.                     | 120               | 130                                 | C. 51                           | Et. 12                        | 39                               |
|          |          | 1/ 2/40  | D.        | O.                     | 80                | 100                                 | C. 45.5                         | Et. 19                        | 26.5                             |
| 48       | 1        | 12/ 8/38 | U.        | E., P.                 | 160               | 210                                 | C. 68                           | Et. 17.5                      | 50.5                             |
|          |          | 12/12/38 | P.D.      | P.                     | 85                | 85                                  | C. 55                           | Et. 12                        | 43                               |
|          |          | 12/20/38 | D.        | P.                     | 20                | 20                                  | C. 40.4                         | Et. 13.8                      | 26.6                             |
| 49       | 3        | 1/12/39  | U.        | P.                     | 90                | 120                                 | C. 45                           | Et. 12                        | 33                               |
|          |          | 1/18/39  | D.        | O.                     | 75                | 80                                  | C. 40                           | Et. 16                        | 24                               |
| 50       | 3        | 1/ 7/39  | U.        | E., T., P.             | 135               | 160                                 | C. 45                           | Et. 5.5                       | 39.5                             |
|          |          | 1/11/39  | P.D.      | P.                     | 135               | 145                                 | C. Blank                        | Et. 13.2                      |                                  |
|          |          | 1/19/39  | D.        | P.                     | 65                | 70                                  | C. 22                           | Et. 12                        | 10                               |
| 51       | 2        | 1/12/39  | D.        | T., P.                 | 245               | 255                                 | C. 37                           | Et. 17                        | 20                               |
| 52       | 2        | 1/28/39  | D.        | E., T., P.             | 185               | 225                                 | C. Blank                        | Et. 15                        |                                  |
|          |          | 2/ 1/39  | D.        | P.                     | 115               | 160                                 | C. 25                           | Et. 10                        | 15                               |
|          |          | 2/ 5/39  | D.        | O.                     | 100               | 150                                 | C. 15                           | Et. ?                         |                                  |
|          |          | 2/ 9/39  | D.        | P.                     | 130               | 160                                 | C. 41                           | Et. 20                        | 21                               |
| 53       | 2        | 1/25/39  | U.        | EE., T., P.            | 185               | 225                                 | C. 32                           | Et. 20                        | 12                               |
|          |          | 1/30/39  | D.        | E., P.                 | 60                | 85                                  | C. 24                           | Et. 5                         | 19                               |
|          |          | 2/ 3/39  | D.        | O.                     | 55                | 60                                  | C. 24                           | Et. 6                         | 18                               |
|          |          | 2/10/39  | D.        | O.                     | 110               | 130                                 | C. 30                           | Et. 6                         | 24                               |
| 54       | 5        | 1/18/39  | U.        | E., T., P.             | 230               | 260                                 | C. 16                           | Et. 13                        | 3                                |
|          |          | 1/22/39  | P.D.      | E., T., P.             | 220               | 260                                 | C. 29                           | Et. 9                         | 20                               |
|          |          | 2/ 1/39  | D.        | E., T.                 | 160               | 200                                 | C. 15                           | Et. 7                         | 8                                |
|          |          | 2/ 5/39  | D.        | E., T.                 | 150               | 180                                 | C. 14                           | Not done                      |                                  |
|          |          | 2/ 9/39  | D.        | E., T.                 | 160               | 185                                 | C. 12.5                         | Not done                      |                                  |
|          |          | 2/16/39  | D.        | E., T.                 | 125               | 140                                 | C. 12                           | Not done                      |                                  |
|          |          | 2/23/39  | D.        | E., T.                 | 85                | 90                                  | C. 12.5                         | Not done                      |                                  |
|          |          | 3/ 2/39  | D.        | E., T.                 | 80                | 95                                  | C. 13                           | Not done                      |                                  |
| 55       | 3        | 11/18/38 | U.        | E., T., P.             | 195               | 230                                 | C. Blank                        | Et. 5                         |                                  |
|          |          | 11/22/38 | P.D.      | E., P.                 | 105               | 125                                 | C. 27                           | Et. 5.4                       | 21.6                             |
|          |          | 11/29/38 | D.        | P.                     | 110               | 150                                 | C. 22                           | Et. 11                        | 11                               |
|          |          | 12/ 6/38 | D.        | P.                     | 85                | 125                                 | C. 50                           | Et. 9.5                       | 41.5                             |
| 56       | 2        | 11/14/38 | P.D.      | E., P.                 | 210               |                                     | C. 31                           | Et. 9                         | 22                               |
|          |          | 11/18/38 | D.        | O.                     | 80                |                                     | C. 20                           | Et. 4.5                       | 15.5                             |
| 57       | 2        | 11/15/38 | U.        | E., T., P.             | 170               | 185                                 | C. 29.8                         | Et. 12                        | 17.8                             |
|          |          | 11/19/38 | P.D.      | T.                     | 80                | 80                                  | C. 25                           | Et. 8.5                       | 16.5                             |
|          |          | 11/29/38 | D.        | T.                     | 85                | 85                                  | C. 23                           | Et. 9.6                       | 13.4                             |
|          |          | 12/ 6/38 | D.        | T., P.                 | 100               | 110                                 | C. Blank                        | Et. 8                         |                                  |
|          |          | 12/12/38 | D.        | T.                     | 95                | 95                                  | C. 28                           | Et. 10                        | 18                               |
| 58       | 2        | 12/ 5/39 | U.        | E., T., P.             | 175               | 190                                 | C. 17                           | Et. 8                         | 9                                |
| 59       | 7        | 12/ 3/38 | U.        | E., P.                 | 110               | 155                                 | C. 19                           | Et. 10                        | 9                                |
| 60       | 2        | 3/30/39  | D.        | O.                     | 80                | 95                                  | C. Blank                        | Et. 9                         |                                  |
|          |          | 4/ 3/39  | D.        | O.                     | 130               | 145                                 | C. 26                           | Et. 15                        | 11                               |
| 61       | 2        | 10/16/39 | D.        | O.                     | 100               | 105                                 | C. 16                           | Et. 8                         | 8                                |
| 62       | 2        | 2/16/39  | U.        | O.                     | 125               | 130                                 | C. 12                           | Et. 8                         | 4                                |
| 63       | 2        | 11/17/38 | D.        | O.                     | 95                | 115                                 | C. 20.6                         | Et. 10.6                      | 10                               |
| 64       | 2        | 11/29/38 | P.D.      | O.                     | 120               | 155                                 | C. 17                           | Et. 8                         | 9                                |

TABLE II—CONT'D

| CASE NO. | ETIOLOGY | DATE     | TREATMENT | SIGNS OF HEART FAILURE | VE-NOUS PRES-SURE | RIGHT UPPER QUAD-RANT COM-PRES-SION | ARM-TO-TONGUE CIRCULA-TION TIME | ARM-TO-LUNG CIRCULA-TION TIME | LUNG-TO-TONGUE CIRCULA-TION TIME |
|----------|----------|----------|-----------|------------------------|-------------------|-------------------------------------|---------------------------------|-------------------------------|----------------------------------|
| 65       | 4        | 10/17/39 | U.        | P.                     | 50                | 50                                  | C. 24                           | Et. 8                         | 16                               |
| 66       | ?        | 4/26/40  | D.        | E., T., P.             | 160               | 180                                 | C. 11.6                         | Et. 5.8                       | 5.8                              |
| 67       | 4        | 7/13/39  | U.        | O.                     | 135               | 160                                 | C. 15                           | Et. 5.5                       | 9.5                              |
|          |          | 7/17/39  | U.        | O.                     | 125               | 125                                 | C. 25                           | Et. 6                         | 19                               |
| 68       | 2        | 5/ 8/39  | U.        | T., P.                 | 120               | 120                                 | C. 34                           | Et. 10                        | 24                               |
| 69       | 1        | 3/19/40  | D.        | T.                     | 100               | 150                                 | M. 13.5                         | Pa. 22<br>0.5 c.c.            |                                  |
| 70       | 3        | 3/16/40  | D.        | T., P.                 | 70                | 80                                  | M. 20                           | Pa. 13<br>1 c.c.              | 7                                |
| 71       | 5        | 3/31/39  | U.        | T.                     | 175               | 200                                 | C. 8.5                          | Et. 4.2                       | 4.3                              |
|          |          | 4/ 5/39  | U.        | T., P.                 | 130               | 145                                 | C. 8                            | Et. 4                         | 4                                |
|          |          | 4/25/39  | D.        | O.                     | 130               | 130                                 | C. 7.4                          | Et. 6                         | 1.4                              |
| 72       | 2        | 3/15/39  | U.        | T., P.                 | 145               | 145                                 | C. 30                           | Et. 10                        | 20                               |
|          |          | 3/21/39  | U.        | T.                     | 80                | 75                                  | C. Blank                        | Et. 10                        |                                  |
| 73       | 2        | 3/15/39  | U.        | E., T., P.             | 120               | 145                                 | C. 15                           | Et. 7                         | 8                                |
|          |          | 3/21/39  | D.        | O.                     | 85                | 95                                  | C. 20                           | Et. 8                         | 12                               |
| 74       | 2        | 2/26/39  | D.        | T., P.                 | 60                | 60                                  | C. 120?                         | Et. 11                        | 109?                             |
|          |          | 3/ 6/39  | D.        | T., P.                 | 60                | 60                                  | C. 35                           | Et. 19                        | 16                               |
|          |          | 4/ 7/39  | D.        | E., P.                 | 150               | 150                                 | C. 32                           | Et. 18                        | 14                               |
| 75       | 2        | 1/26/39  | U.        | EE., T., P.            | 220               | 280                                 | C. 18                           | Et. 9.5                       | 8.5                              |
|          |          | 1/31/39  | P.D.      | E., T., P.             | 100               | 180                                 | C. 17                           | Et. 9.6                       | 7.4                              |
|          |          | 2/ 4/39  | D.        | P.                     | 40                | 100                                 | C. 11                           | Et. 5                         | 6                                |
|          |          | 2/11/39  | D.        | O.                     | 45                | 45                                  | C. 11                           | Et. 5                         | 6                                |
| 76       | 4        | 11/21/39 | P.D.      | T., P.                 | 140               | 140                                 | C. 57                           | Et. 20                        | 37                               |
| 77       | 2        | 3/24/39  | P.D.      | P.                     | 115               | 130                                 | C. 23                           | Et. 8                         | 15                               |
| 78       | 4        | 11/24/39 | D.        | O.                     | 60                | 60                                  | M. 19                           | Et. 9                         | 10                               |
| 79       | 1        | 7/10/40  | D.        | O.                     | 290               |                                     | C. 30.4                         | Et. 16.8                      | 13.6                             |
| 80       | 2        | 8/13/40  | P.D.      | EE., T., P.            | 165               | 315                                 | C. 45                           | Et. 25                        | 20                               |
| 81       | 2        | 8/21/40  | P.D.      | E.                     | 180               | 210                                 | M. 22.8                         | Et. 11                        | 11.8                             |
| 82       | 2        | 9/14/40  | P.D.      | EE., T., P.            | 280+              | ?                                   | C. 28                           | Et. 12                        | 16                               |
| 83       | 1        | 9/ 6/40  | D.        | E., P.                 | 150               | 175                                 | C. 35.8                         | Et. 16                        | 19.4                             |
|          |          | 9/11/40  | D.        | E.                     | 95                | 115                                 | C. 16                           | Et. 6.8                       | 9.2                              |
| 84       | 3        | 7/16/40  | D.        | E., P.                 | 200               | 230                                 | M. 30                           | Et. 15                        | 15                               |
| 85       | 4        | 7/31/40  | D.        | O.                     | 158               | 165                                 | M. 19.6                         | Et. 10                        | 9.6                              |
| 86       | 2        | 7/11/40  | U.        | P.                     | 160               | 175                                 | M. 24                           | Et. 15                        | 8                                |
| 87       | 1        | 7/ 8/40  | D.        | O.                     | 150               | 155                                 | M. 19                           | Et. 12.6                      | 6.4                              |
| 88       | 2        | 7/ 9/40  | U.        | E., P.                 | 180               | 200                                 | M. 21                           | Et. 9                         | 12                               |
|          |          | 8/ 2/40  | D.        | O.                     | 120               | 130                                 | M. 16                           | Et. 9                         | 7                                |
| 89       | 3        | 9/ 6/40  | P.D.      | E., P.                 | 190               | 220                                 | M. 26                           | Et. 12.2                      | 13.8                             |
| 90       | 1        | 7/19/40  | D.        | O.                     | 140               | 150                                 | M. 22                           | Et. 12.2                      | 9.8                              |
| 91       | 2        | 8/13/40  | U.        | E.                     | 160               | 175                                 | M. 19                           | Et. 10                        | 9                                |
| 92       | 2        | 8/20/40  | D.        | O.                     | 135               | 135                                 | M. 23                           | Et. 9                         | 14                               |
| 93       | 2        | 7/11/40  | D.        | E.                     | 140               | 155                                 | M. 17                           | Et. 13.4                      | 3.6                              |
| 94       | 2        | 7/13/40  | P.D.      | E., P.                 | 200               | 225                                 | M. 60                           | Et. 42                        | 18                               |
| 95       | 2        | 7/12/40  | D.        | E.                     | 160               | 170                                 | M. 30                           | Et. 12.6                      | 17.4                             |
| 96       | 3        | 8/25/40  | U.        | E., P.                 | 160               | 180                                 | M. 65.2                         | Et. 22.4                      | 42.8                             |
| 97       | 3        | 9/ 6/40  | D.        | E., P.                 | 200               | 230                                 | M. 38                           | Et. 15                        | 23                               |
| 98       | 4        | 8/31/40  | D.        | E., P.                 | 100               | 110                                 | M. Blank                        | Et. 13                        |                                  |
| 99       | 2        | 8/ 9/40  | D.        | E., P.                 | 210               | 235                                 | M. 65?                          | Et. 14                        |                                  |
| 100      | 4        | 8/ 7/40  | P.D.      | O.                     | 50                | 50                                  | M. 21.8                         | Et. 10                        | 11.8                             |

1, Rheumatic heart disease; 2, hypertensive heart disease; 3, syphilitic heart disease; 4, coronary arteriosclerosis; 5, hyperthyroid heart disease; 6, beriberi heart disease; 7, severe anemia. U., Untreated; P.D., partially digitalized; D., completely digitalized; E., edema; EE., anasarca; T., tachycardia; P., pulmonary congestion; O., none; C., calcium gluconate; Et., ether; M., magnesium sulfate; Pa., paraldehyde.

after a patient with heart failure has been treated with rest in bed or digitalis, or both, it is not uncommon to find that the measurements are within normal limits. There were four such cases in the group of 100 cases. This fact serves to emphasize that estimations of the venous pressure and circulation time should be made early and repeatedly if they are to have full diagnostic value, particularly in cases of mild heart failure.

Isolated failure of the right ventricle, in our experience, has been rare. There were no such cases in our series. This type of heart failure is said to cause elevation of the venous pressure and prolongation of both the arm-to-lung and arm-to-tongue circulation time, but the lung-to-tongue circulation time is not prolonged.<sup>2</sup> In this connection, thirty-four of the patients with general heart failure had measurements within normal limits for the lung-to-tongue circulation time. Thirty-seven such measurements were obtained in these cases. This seems to impair, on theoretical grounds, the value of the lung-to-tongue circulation time measurement in the diagnosis of isolated right ventricular failure.

It is interesting that, in a considerable number of instances, edema was absent, in spite of the fact that the venous pressure was abnormal. There were twenty-three instances of this type in which the venous pressure was above 150 mm. of saline; the highest measurement was 275 mm. In addition, there were forty-three instances in which the initial venous pressure measurement was within normal limits, but compression of the abdomen indicated persistence of right ventricular failure. There were two other instances of this latter type that are difficult to evaluate because the other measurements were normal and signs of heart failure had disappeared. These facts would seem to demonstrate that a careful measurement of the venous pressure is a reasonably accurate method of detecting the presence of right ventricular failure when other signs are lacking.

In cases in which the venous pressure and circulation times are measured repeatedly during the course of heart failure, the progress of the patient can be followed objectively. This manner of using the circulation tests can best be exemplified by illustrative cases.

#### CASE REPORTS

CASE 2.—The patient was a 64-year-old white man who was in the hospital for seventeen days because of heart failure due to hypertensive heart disease. On the day of admission his venous pressure was 250 mm. of saline, and it rose to 300 mm. with abdominal compression. The arm-to-tongue circulation time was twenty-two seconds; the arm-to-lung time, seven seconds. At this time there was evidence of pulmonary congestion and moderate edema. Four days later, when the patient was partially digitalized, the signs of heart failure had subsided except for slight edema. On this day the only abnormality in the circulation measurements was a significant rise of the venous pressure from 130 mm. to 150 mm. during abdominal compression.

By the time the patient was fully digitalized all evidence of heart failure had disappeared. The venous pressure and circulation times were entirely normal within two weeks of the day of admission.

In this case the measurements under discussion afforded confirmatory evidence of the progressive improvement of the patient. The final readings indicated that he had recovered completely from this attack of heart failure.

CASE 1.—The patient was a 39-year-old colored woman with long-standing rheumatic heart disease. There was evidence of involvement of the aortic and mitral valves. At the time of her admission to the hospital she was thought to have moderately severe heart failure, as indicated by the usual signs. At this time the circulation measurements were as follows: venous pressure, 150 mm., rising to 180 mm., with abdominal compression; arm-to-tongue circulation time, 26.5 seconds; arm-to-lung circulation time, eleven seconds.

By the fifth hospital day the patient was partially digitalized and appeared somewhat improved. However, the measurements showed little change. The venous pressure was 185 mm., and rose to 250 mm. with abdominal compression, and the arm-to-tongue and arm-to-lung circulation times were, respectively, forty-eight seconds and nine seconds. By the time the patient had been in the hospital for two weeks and was fully digitalized the measurements still failed to show significant improvement, and, at the end of three weeks, they could be interpreted as indicating aggravation of the heart failure. At this time the venous pressure was 220 mm., and rose to 300 mm. with compression of the abdomen, and the circulation times were sixty-five seconds and eighteen seconds.

In this case these measurements provided a means of demonstrating that the patient's heart failure was essentially unchanged at a time when she seemed otherwise to be improving. They further showed, objectively, the tendency of the heart failure to grow steadily worse. When values of this type are obtained on a patient with uncomplicated heart failure, the prognosis is almost uniformly quite grave.

CASE 52.—This patient was a 67-year-old white man; he had hypertensive heart disease with cardiac enlargement, auricular fibrillation, and heart failure. He had been digitalized because of heart failure some months before admission to the hospital, and had been taking a daily maintenance dose of digitalis. However, symptoms and signs of heart failure reappeared, and, at the time of entrance to the hospital, the patient was dyspneic and edematous. Circulation measurements on the first hospital day confirmed the diagnosis of general heart failure. The venous pressure was 185 mm. of saline, and rose to 225 mm. with abdominal compression. The arm-to-tongue circulation time was not measured because calcium gluconate failed to produce a sensation of warmth. The arm-to-lung circulation time was fifteen seconds. The patient improved during the ensuing week, with rest in bed, the administration of diuretics, and restriction of liquid and salt intake. On the fourth hospital day the circulation measurements were more nearly normal, and, on the eighth hospital day, the only remaining abnormality was a significant rise of the venous pressure (from 100 mm. to 150 mm.) with abdominal compression. By this time the patient felt very well, and all signs of heart failure had disappeared. It was therefore deemed safe to allow him to begin some activity. The fallacy of this judgment was well demonstrated by the final measurements which were obtained after resumption of slight activity. The venous pressure was 130 mm., and rose to 160 mm. with compression of the abdomen. Both the arm-to-lung and arm-to-tongue circulation times were prolonged to twenty seconds and forty-one seconds, respectively.

This case further demonstrates the utility of objective methods of estimating the state of cardiac hemodynamics. The effect of resumption of physical activity on the patient with heart failure can best be judged by the use of such methods. This is especially true in the case of patients with heart failure for whom a protracted period of rest in bed is prescribed. Such patients commonly experience breathlessness and weakness on first getting out of bed. It is then hard to ascertain, except by measurements of the venous pressure, circulation time, or vital capacity, whether these symptoms are the result of recurring heart failure or of the kind of physical atony which follows long rest in any disease.

CASE 3.—This patient was a 29-year-old negro who entered the hospital because of hypertensive heart disease with heart failure. On the day after admission, with the patient partially digitalized, the only remaining physical evidence of heart failure was tachycardia. On this day the venous pressure was 120 mm., and rose to 130 mm. with abdominal compression; the arm-to-tongue circulation time was twenty-six seconds; and the arm-to-lung time was seven seconds. The patient remained in the hospital for ten days and was discharged as improved.

The circulation measurements in this case were more or less typical for isolated left ventricular failure. It should be re-emphasized that measurement of the arm-to-tongue circulation time is the only one of the methods under discussion which will confirm the diagnosis of isolated failure of the left ventricle.

#### DISCUSSION

Perusal of the results of the circulation measurements in this series of 100 cases reveals certain discrepancies. Not all of these discrepancies are easily explained, and this probably would be true in any study of similar magnitude. For example, in a number of instances the venous pressure was found to be high, although the circulation time measurements were within normal limits. This kind of discrepancy has already been mentioned in the analysis of cases of general heart failure, where it was pointed out that in thirty-three cases the arm-to-lung circulation time was normal, although the venous pressure measurement indicated the presence of right ventricular failure. In addition, there were twenty-two cases in which the arm-to-tongue circulation time was normal in spite of the fact that the venous pressure and other manifestations indicated that heart failure was present. Three of these twenty-two patients had hyperthyroid heart disease.<sup>3</sup> The remaining nineteen cases included all the other etiological types in the series except beriberi heart disease. It should be mentioned, however, that measurements of this kind were much more constantly present in the cases of hyperthyroid heart disease than in the other cases. It is interesting that none of the measurements were of this type in the two cases of beriberi heart disease in our series. This is mentioned only because beriberi heart disease is considered to be an important cause of elevation of the venous pressure in the presence of a normal circulation time.<sup>4</sup>

There were a number of instances in the series in which the venous pressure was normal but the circulation time was prolonged. This has already been discussed above, in connection with isolated left ventricu-

lar failure. However, in fifteen other cases, both the arm-to-lung and arm-to-tongue circulation times were slightly longer than normal, although the venous pressure was unaffected. This occurred in every case at a time when all other manifestations of heart failure had disappeared. It is therefore difficult to explain except as the result of error due to human fallibility, or by assuming that in some instances the circulation time may exceed the figure accepted as the upper limit of normal without indicating that heart failure is present.

It has been our experience that difficulties in the interpretation of the circulation measurements arise mainly from errors in technique. Since cooperation by the patient is indispensable if accurate measurements are to be secured, sufficient time must be taken beforehand to explain exactly what the patient must do. In this connection, the rate and character of respiration are very important. The patient may hold his breath or breathe too rapidly during measurement of the circulation time. Irregular breathing is especially common when ether is used for the arm-to-lung time, because of the pain which is sometimes felt along the course of the injected vein. Even when the patient is forewarned, such pain may cause him to hold his breath momentarily, thereby detracting from the accuracy of the measurement. In the same way, talking or coughing by the patient may significantly alter the results.

Excessive nervousness on the part of the patient may interfere with the measurements. It is essential that he be quiet during the procedure, especially if an accurate estimation of the venous pressure is to be obtained. Obviously, mental aberration or coma may prevent employment of those parts of the procedure which require active cooperation by the patient. An example is the measurement of the arm-to-tongue circulation time by means of calcium gluconate or magnesium sulfate.

The presence of hyperthyroidism may give rise to apparent discrepancies.<sup>3</sup> In this condition, circulation time measurements may vary considerably, depending upon the severity of the hyperthyroidism and whether or not heart failure is present. Even with severe heart failure, the velocity of blood flow may remain relatively normal in the hyperthyroid patient. In general, therefore, estimation of the venous pressure is the only part of the procedure which is reliable for detecting the presence and following the course of hyperthyroid heart disease. The same is true, but to a lesser degree, in beriberi heart disease,<sup>4</sup> heart failure due to severe anemia,<sup>5</sup> and heart failure complicated by high fever.<sup>3</sup>

Pleural, pulmonary, or mediastinal disease sometimes interferes with the accuracy of the circulation measurements. Pleural or pulmonary disease of a type which alters the intrathoracic pressure may produce changes in the venous pressure and circulation time. However, lesions of this character usually give obvious physical signs, so that confusion in the interpretation of the results of measurements of the venous pres-

sure and circulation time is unlikely. On the other hand, mediastinal lesions, particularly aneurysm or other tumor, may cause remarkable alterations in the venous current in the upper extremities by compressing the superior vena cava or one of its tributaries, and, at the same time, may escape notice in the course of the usual physical examination.<sup>6</sup> Such lesions, therefore, may occasionally lead to misinterpretation of the circulation measurements. This is also true, but more rarely, in cases of obstruction of the peripheral veins.

There is some variation in the results of measurement of the circulation time, depending on the nature and amount of the substance employed. This is even more pronounced when the velocity of blood flow is diminished, as, for example, in heart failure. For measurement of the total circulation time, 5 c.c. of a 20 per cent calcium glueonate solution and 5 to 6 c.c. of a 10 per cent magnesium sulfate solution apparently give equally good results. Early in the course of our study we employed 2.5 c.c. of a 20 per cent calcium glueonate solution, but this amount commonly failed to produce a reaction in patients with a prolonged circulation time. Therefore, the larger dose of 5 c.c. is now usually employed. Paraldehyde is much less reliable than ether for measurement of the arm-to-lung circulation time.<sup>7</sup> Furthermore, the accuracy of the test with ether is enhanced if the operator attempts in each case to verify the end point by smelling the patient's breath for the odor of the drug. No serious reaction occurred as the result of administering any of the drugs used in the study.

The wide range of the normal limits for the circulation time measurements is another factor which theoretically may account for some difficulty in accurate interpretation of results. For example, an arm-to-tongue circulation time of sixteen seconds may be normal for one patient and indicative of heart failure in another. This fact constitutes an important argument for the use of more than one method in the study of a patient with heart failure. The other reasons for using more than one method have already been implied and include mainly the apparent discrepancies observed in some cases of general heart failure in which the venous pressure is abnormally elevated and the circulation time normal, or vice versa. From our results, it may safely be judged that, if the venous pressure and arm-to-tongue circulation time are measured in each case of cardiac failure, failure to obtain an accurate estimate of the state of cardiovascular hemodynamics will be rare. Probably the arm-to-lung circulation time measurement is less important except in rare etiological types of heart disease. Although the range of normal limits for the venous pressure also is wide, less difficulty is experienced in the interpretation of measurements near the upper limit of normal because of the added information secured when the effect on the venous pressure of compression of the abdomen is observed.

Venous pressure measurement might well serve as the sole objective test for heart failure if it were not for the fact that it is unaffected in cases of isolated left ventricular failure.

While our main inquiry in this study was with reference to the use of circulation measurements in cases of heart failure, other cases naturally crept in. These were all cases in which heart failure was suggested by one or more prominent symptoms. These cases are mentioned in order to emphasize the further utility of the objective methods in ruling out cardiac failure. This negative value of the methods is as important in many respects as their positive value in the diagnosis and study of heart failure, and subsequent clinical developments confirmed the fact that the diagnosis of heart failure was erroneous. Thus, such manifestations as dyspnea, râles at the bases of the lungs, cough, peripheral edema, tachycardia, cardiac enlargement, hypertension, hyperthyroidism, signs of syphilitic heart disease, and signs of rheumatic heart disease may be confusing diagnostically under some conditions. In all of the cases under consideration here, the venous pressure and circulation time measurements were found to be normal.

#### SUMMARY AND CONCLUSIONS

1. The results of simultaneous measurements of the arm-to-lung and arm-to-tongue circulation times and of the venous pressure in 100 consecutive cases of heart failure are presented.

2. These results show that, in general heart failure, the venous pressure is abnormally elevated or shows a significant rise when the abdomen is compressed, and that the circulation times are usually prolonged. When improvement occurs in this type of heart failure, the arm-to-tongue circulation time may nevertheless remain prolonged for an unpredictable period after all other signs of heart failure have disappeared. This presumably indicates the persistence of left ventricular failure.

3. In seven cases of the series the clinical observations were indicative of isolated left ventricular failure during the entire time the patients were under observation. In these cases the venous pressure and arm-to-lung circulation time were normal, but the arm-to-tongue circulation time was prolonged.

4. In thirty-four cases of general heart failure the lung-to-tongue circulation time was within normal limits. This tends to impair, on theoretical grounds, the value of this measurement in the diagnosis of isolated right ventricular failure.

5. In cases of heart failure, the venous pressure may be abnormally high or rise significantly with abdominal compression when other signs of failure of the right ventricle are lacking.



6. Repeated measurements of the venous pressure and circulation time in cases of heart failure afford a means of following the course of the heart failure objectively.

7. Combined measurements of the venous pressure and circulation time are necessary in cases of heart failure for perfect diagnostic appraisal.

8. When there are symptoms suggestive of heart failure, but none is actually present, the circulation measurements are in many respects as valuable in ruling it out as they are in diagnosing and studying it.

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## THE ACTION OF ANGIOTONIN ON THE COMPLETELY ISOLATED MAMMALIAN HEART

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WITH increasing evidence<sup>1-6</sup> that renin is the probable humoral agent in experimental renal hypertension, the action of this substance at any point in the cardio-renal-vascular complex grows in interest.

Hill and Andrus<sup>7</sup> reported a series of experiments in which the effects of renin and angiotonin (activated renin<sup>8</sup>) were studied on cat hearts perfused with Ringer-Loeke solution by the Langendorff method. Renin, because of the absence of renin-activator<sup>8, 9</sup> from the perfusion medium, was found to be without effect. Angiotonin, on the other hand, produced a marked reduction in coronary flow, followed often by a late rise. The former effect was undiminished with subsequent injections into the same preparation, whereas the latter was reduced. The amplitude of the beat increased markedly; the change followed that in coronary flow, and often outlasted it. Successive injections showed undiminished effectiveness in this regard. A slight slowing of the heart rate was sometimes noted at the time of the decrease in coronary flow.

The experiments to be reported were undertaken in an effort to examine in greater detail the action of angiotonin on the completely isolated mammalian heart, with particular regard to its effect on cardiac work and efficiency.

### METHODS

Six experiments were done on the completely isolated, blood-perfused, cat heart, according to the technique described by Moe and Visscher,<sup>10</sup> but modified for use with smaller mammals (Fig. 1). Oxygen utilization was measured continuously in a closed system of suitable dimensions and sensitivity. The filling and emptying pressures of the heart were controlled, but the diastolic volume was permitted to decrease with the administration of the angiotonin, for an efficiency increase at a smaller diastolic volume and nearly constant filling pressure is even more significant than an increase of efficiency at higher filling pressures and constant diastolic volume would be.

Six preliminary experiments were done, two with the dog heart-lung preparation, one with the completely isolated dog heart, and three with the completely isolated cat heart. Oxygen utilization and cardiac efficiency were not ascertained in these experiments.

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In all experiments on the cat, one animal served as both blood donor and subject. Heparin was used as the anticoagulant. Angiotonin was injected into the perfusion medium in amounts varying from 0.01 to 0.10 c.c.

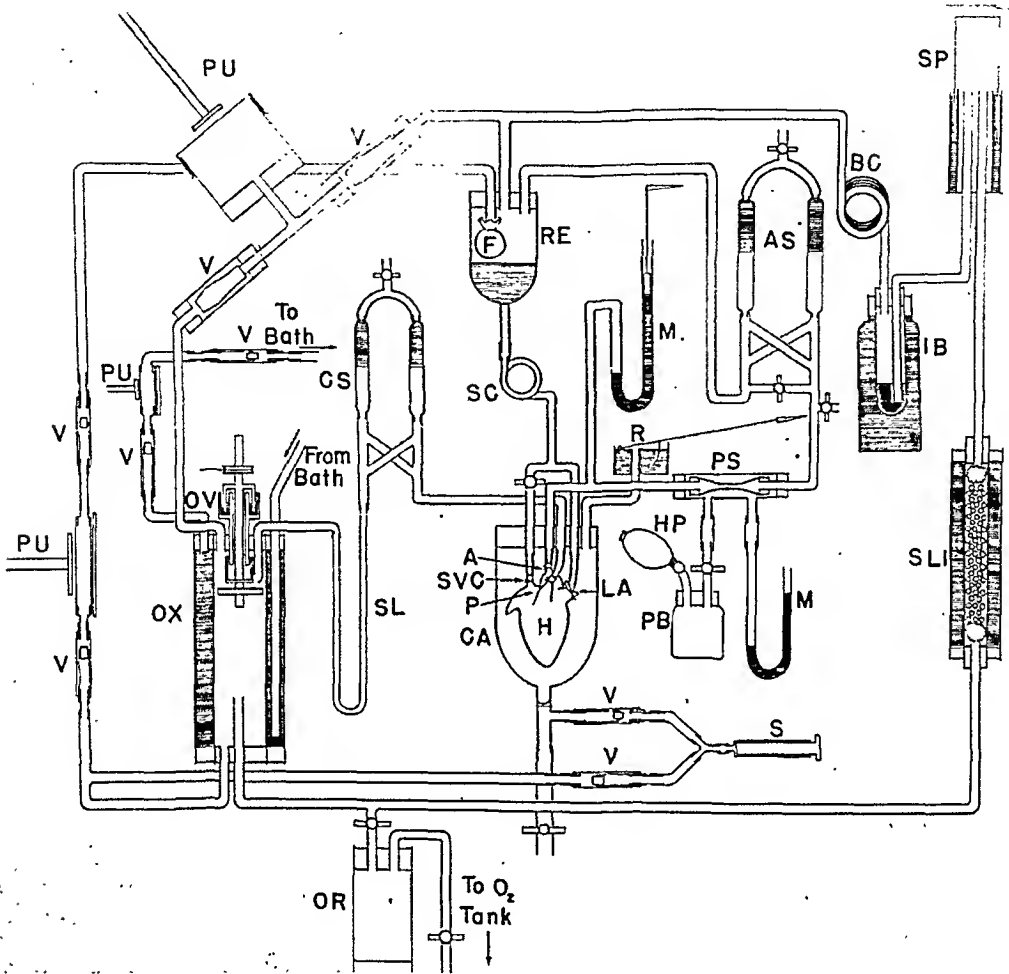


Fig. 1.—A, brachiocephalic artery; AS, aortic stromuhr; BC, brass warming coil; CA, cardiometer; CS, coronary stromuhr; F, filter; H, heart; HP, hand pump; IB, indicator bottle; LA, left atrium; M, mercury manometer; OR, oxygen reservoir for warming O<sub>2</sub> before admitting to the system; OV, oil-sealed valve; OX, oxygenator; P, pulmonary artery; PU, pump; PB, pressure bottle; PS, pressure sleeve; R, small spirometer for recording changes in heart size; RE, blood reservoir; S, syringe for withdrawing drainage fluid and returning to the system; SC, silver warming coil; SL, silver loop for warming blood entering oxygenator from coronary stromuhr; SLI, soda and lime chamber; SP, spirometer; SVC, superior vena cava; V, valve. The cardiometer, pressure sleeve, silver coil, silver loop, brass coil, and oxygen reservoir are immersed in a constant temperature bath. The soda and lime chamber, indicator bottle, and oxygenator are placed in a water jacket. The jacket surrounding the oxygenator is circulated with water from the bath. The diagram is not drawn to scale.

## RESULTS

### CORONARY FLOW

In the ten isolated heart experiments in which coronary flow was studied, a decrease varying from a small fraction of the total, to complete arrest of flow, in one instance, was noted. In only one case was there no effect (Experiment 11, Table I). In this instance the first two doses were minute (0.01 to 0.02 c.c. of a less active preparation),

but the third was larger (0.10 c.c.). The possibility exists that a transient effect might have occurred between measurements.

TABLE I

THE EFFECT OF ANGIOTONIN ON THE COMPLETELY ISOLATED MAMMALIAN HEART

| EX-<br>PERI-<br>MENT<br>NO. | ANIMAL | DOSE<br>(C.C.)           | PER CENT<br>DECREASE IN<br>CORONARY<br>FLOW<br>(MAX.) | DURATION<br>OF<br>CORONARY<br>FLOW<br>EFFECT<br>(MIN.) | PER CENT<br>INCREASE<br>IN CARDIAC<br>WORK<br>(MAX.) | PER CENT<br>INCREASE<br>IN CARDIAC<br>EFFICIENCY<br>(MAX.) | DURATION<br>OF<br>EFFICIENCY<br>EFFECT                                   |
|-----------------------------|--------|--------------------------|---|--|--|--|--|
| 7                           | Cat    | 0.05                     | 100% at-<br>tained in<br>2 min.                       | 3  | 66% at-<br>tained in<br>5 min.                       | 56% at-<br>tained in<br>5 min.                             | Still ele-<br>vated by<br>27%, 13<br>min. fol-<br>lowing an-<br>giotinin |
| 8                           | Cat    | 0.05                     | 91% at-<br>tained in<br>1 min.                        | 6  | 73% at-<br>tained in<br>6 min.                       | 49% at-<br>tained in<br>6 min.                             | 14 min.  |
| 9                           | Cat    | 0.05                     | 64% at-<br>tained in<br>3.5 min.                      | 6  | 305% at-<br>tained in<br>5.5 min.                    | 317% at-<br>tained in<br>6 min.                            | Still ele-<br>vated by<br>35%, 22<br>min. fol-<br>lowing an-<br>giotinin |
| 10                          | Cat    | 0.03                     | 71% at-<br>tained in<br>1 min.                        | 3  | 45% at-<br>tained in<br>3 min.                       | 44% at-<br>tained in<br>3 min.                             | 28 min.  |
| 11                          | Cat    | 0.01*<br>0.02*†<br>0.10* | Decrease not<br>observed                              |  | 20% at-<br>tained in<br>53 min.                      | 15% at-<br>tained in<br>53 min.                            | Still ele-<br>vated by<br>11%, 73<br>min. fol-<br>lowing an-<br>giotinin |
| 13                          | Cat    | 0.02                     | 14% at-<br>tained in<br>2 min.                        | 9  | 5.2% at-<br>tained in<br>2 min.                      | 5.8% at-<br>tained in<br>2 min.                            | 6 min.   |

\*A less active solution of angiotonin used in this experiment.

†A small, transient decrease in diastolic volume observed.

Coronary flow effects appeared quite promptly and lasted only a few minutes. In eleven trials, flow returned to slightly supernormal values in five, slightly subnormal, in four, and to the same level, in two. In one experiment in which three successive trials with the same dose yielded a decrease in flow, this effect diminished progressively.

#### DIASTOLIC VOLUME EFFECT

In every instance but one, the injection of angiotonin was followed by a fall in diastolic volume which came on promptly and lasted from five minutes to over an hour. Larger doses provoked a response which was greater in both amplitude and duration. When coronary flow restriction was marked, a transient dilatation preceded the diminution in

heart size, or interrupted it momentarily, and coincided with the moment of greatest restriction in coronary flow.

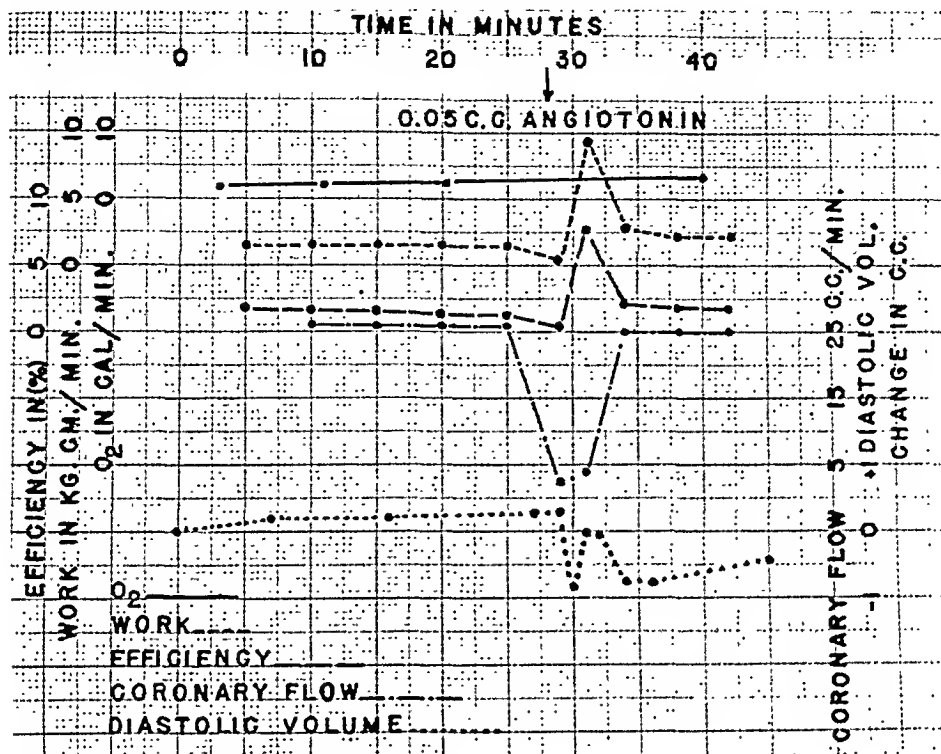


Fig. 2.—Graphic presentation of a typical experiment (Experiment 8, Table I).

The failure to obtain a decrease in diastolic volume occurred in the experiment cited previously (Experiment 11, Table I), and with a dose (0.01 c.c.) that was ineffective in eliciting either an increase in cardiac efficiency or a decrease in coronary flow. In the next trial in the same experiment, a dose (0.02 c.c.) which was incapable of exerting a detectable coronary or efficiency effect did produce a transient decrease in diastolic volume.

#### CARDIAC WORK, OXYGEN UTILIZATION, AND EFFICIENCY

In the six experiments in which these factors were studied, work was found to increase from 5 to 305 per cent within a few minutes of the administration of angiotonin, and remained elevated from several minutes to over an hour.

In the period after the injection of angiotonin, in all six experiments, it was found that oxygen utilization attained supernormal levels, whereas diastolic volume still remained below the control volume. In spite of this, efficiency increases of considerable magnitude, roughly paralleling those which occurred in work, were noted.

In Experiment 11, Table I, it will be noted that the first two trials did not produce a change in coronary flow, work, or efficiency, and, in

Experiment 13, Table I, the smallest observed decrement in coronary flow (except for Trial 3, Experiment 11, in which no decrease was observed) occurred with the smallest observed increment in work and efficiency.

Too much significance cannot be attached to the occurrence of an efficiency effect in the absence of a decrease in coronary flow, as in Trial 3 of Experiment 11 (Table I). As already stated, it is not impossible that a transient fall in coronary flow might have occurred between readings. It is of interest, however, that in Trial 2 of this same experiment, although no changes in coronary flow, cardiac work, or efficiency were detectable, a transient decrease in diastolic volume was in evidence, indicating some effect on the myocardium.

Table I summarizes the salient features of this group of experiments.

#### HEART RATE

The usual response was a slight slowing which was coincident with the decrease in coronary flow.

#### DISCUSSION

Although no exact parallelism between the effects of angiotonin on the coronary vessels and myocardium has been observed with larger doses, both effects decreased in intensity and disappeared as the dosage was diminished. In two cases in which one effect may have been elicited independently of the other, it was the coronary effect that was not observed.

Although one would hesitate to transfer conclusions drawn from experiments of this type to the intact animal, the fact that the vasoconstrictor and efficiency-increasing properties of angiotonin disappear with about the same dose under controlled conditions suggests that, if the substance is liberated in vivo in sufficient quantity to exert one effect, it will probably exert the other, as well.

#### CONCLUSIONS

Angiotonin, when injected into the completely isolated cat heart, causes (1) constriction of the coronary arteries, (2) a decrease in the diastolic volume of the heart, and (3) an increase in the oxygen consumption, external work, and efficiency of the heart.

The author wishes to thank Dr. Irvine H. Page for suggesting these studies and for furnishing the angiotonin solutions and Dr. M. B. Visscher for his kind interest and help.

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# THE AUTONOMIC MECHANISM OF HEAT CONSERVATION AND DISSIPATION

## II. EFFECTS OF COOLING THE BODY

### A COMPARISON OF PERIPHERAL AND CENTRAL VASOMOTOR RESPONSES TO COLD

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IN A PREVIOUS communication<sup>1</sup> we reported the effects on skin temperature of exposing the body to heat. Our studies were carried out on patients who had been subjected to various operations on the sympathetic nervous system. The operations were mostly unilateral, and this provided the opportunity for control studies on the normally innervated side. The present report is concerned with the effects on skin temperature of cooling the entire body in a refrigerator.

It might be supposed that under the conditions of these experiments the skin loses heat as an inanimate body. The presence of circulating blood in the skin, however, makes this impossible. The temperature of viable skin at all times is a function of the temperature of the blood and of the factors which control its rate of flow through the cutaneous vessels. To secure data relevant to this problem was the purpose of these experiments.

#### METHOD

The patient was exposed for twenty to thirty minutes, and basal temperatures of the skin were taken at room temperature. The patient was then placed in a refrigerator\* and seated in a chair on a square of blanket, remaining exposed except for a loincloth. The heels of the subject rested on a box, leaving the remainder of the feet exposed. The skin temperatures were followed at intervals, as well as the mouth temperature, blood pressure, and pulse rate. Other observations, such as pilomotor activity, shivering, and the appearance of skin, were recorded.

The skin temperatures were taken with a Tyco dermaterm.<sup>†</sup> The temperature of the junction thermocouple was checked for each set of readings, and the readings were corrected for any slight change in the temperature of the junction thermocouple. Only the relative changes in skin temperature are recorded in the tables. More patients were studied than are reported here, but these are representative.

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\*We wish to thank Dr. Elmer DeGowin, of the Department of Medicine, for allowing us the free use of the blood bank refrigerator.

<sup>†</sup>Taylor Instrument Company, Rochester, N. Y.



The patients reported here did not have vasospastic disorders, except that Buerger's disease (Richard W., Experiment 7) may be associated with an abnormal degree of vasospasm.

*Experiment 1.*—March 7, 1940. Leah C., aged 33, 379 days after section of the anterior and posterior roots from T 1 to T 5, inclusive, on both sides, and anterior chordotomy at T 3 on both sides, and forty-eight days after removal of the inferior cervical and first dorsal ganglia on the right (Table I).

TABLE I  
EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE ( ° C.) |      |  |                      |      |                       |      |                       |         |        |         |
|-------------------|--------------------------|------|--|----------------------|------|-----------------------|------|-----------------------|---------|--------|---------|
|                   | RIGHT                    | LEFT |  | RIGHT                | LEFT | RIGHT                 | LEFT | RIGHT                 | LEFT    | RIGHT* | LEFT*   |
| Forehead          | 6.0                      | 6.5  |  | 0.5                  | 1.5  | -0.5                  | 1.5  | -1.5                  | 1.0     | -7.5   | -5.5    |
| Nose              | 5.0                      | 5.0  |  | 0.0                  | 0.0  | -1.0                  | -1.0 | -1.5                  | -1.5    | -6.5   | -6.5    |
| Ears              | 5.0                      | 5.5  |  | 1.0                  | 1.5  | -1.0                  | -1.0 | -1.5                  | -1.5    | -6.5   | -7.0    |
| Cheek             | 6.0                      | 5.5  |  | 1.0                  | 0.0  | -0.5                  | -1.5 | -1.5                  | -2.5    | -7.5   | -8.0    |
| Neck              | 7.0                      | 7.0  |  | 4.0                  | 4.0  | 2.5                   | 3.0  | 1.5                   | 1.5     | -5.5   | -5.5    |
| Chest             | 6.5                      | 7.0  |  | 2.0                  | 1.5  | 1.0                   | 0.5  | 0.0                   | 0.5     | -6.5   | -7.5    |
| Arm               | 6.5                      | 6.0  |  | 1.5                  | 1.0  | 0.0                   | 1.5  | -2.0                  | -1.5    | -8.5   | -7.5    |
| Forearm           | 6.5                      | 6.0  |  | 2.0                  | 1.5  | 0.0                   | 0.0  | -1.0                  | -1.0    | -7.5   | -7.0    |
| Palm              | 6.5                      | 5.5  |  | 2.5                  | 0.0  | 0.0                   | -2.0 | -2.0                  | -4.0    | -8.5   | -9.5    |
| Finger            | 6.0                      | 1.0  |  | 1.0                  | -6.5 | -3.5                  | -9.0 | -7.0                  | (-10.0) | -13.0  | (-11.0) |
| Abdomen           | 6.0                      | 6.5  |  | 1.0                  | 1.0  | -0.5                  | 0.0  | -1.5                  | -2.0    | -7.5   | -8.5    |
| Thigh             | 5.5                      | 5.0  |  | 0.0                  | -0.5 | -1.5                  | -2.0 | -2.0                  | -2.5    | -7.5   | -7.5    |
| Calf              | 4.5                      | 4.5  |  | -1.0                 | -1.5 | -2.0                  | -3.0 | -2.5                  | -3.5    | -7.0   | -8.0    |
| Ankle             | 4.5                      | 5.0  |  | -0.5                 | 0.0  | -2.0                  | -2.0 | -3.0                  | -3.0    | -7.5   | -8.0    |
| Toe               | 2.0                      | 2.0  |  | -5.0                 | -5.0 | -8.0                  | -8.0 | -8.5                  | -8.5    | -10.5  | -10.5   |
| Mouth temperature | 37.22° C.<br>99.0° F.    |      |  | 37.0° C.<br>98.7° F. |      | 36.75° C.<br>98.2° F. |      | 36.40° C.<br>97.5° F. |         |        |         |
| B. P.             | 180/118                  |      |  | 190/130              |      | 186/124               |      | 190/130               |         |        |         |
| Pulse rate        | 72                       |      |  | 84                   |      | 72                    |      | 84                    |         |        |         |
| Time (P.M.)       | 3:35                     |      | 3:45                                       | 3:55                 |      | 4:05                  |      | 4:15                  |         |        |         |
| Remarks           | Basal                    |      | En-<br>ters<br>re-<br>frig-<br>era-<br>tor |                      |      |                       |      |                       |         |        |         |

\*Last two columns show differences between first and last readings.  
( ) The readings in parentheses should be greater (colder), for the needle of the instrument deflected somewhat off the scale.  
Room temperature, 23.5° C.; temperature of refrigerator, 5.0° C.

*Observations and Comment.*—The readings at room temperature showed a significant difference on the two sides only on the palms and fingers; the right (denervated) middle finger was 5° warmer. At the end of the experiment the right finger was 13° cooler, but was still over 3° warmer than the left, which was 11 degrees cooler. The right hand felt subjectively warm throughout the experiment, whereas the left ached with cold. The right (denervated) hand became only slightly flushed, but the normal hand soon became markedly flushed and, later, dusky.

We feel that this experiment is significant only in relation to the cervicodorsal ganglionectomy. The section of the anterior roots from T 1 to T 5 abolished thermoregulatory sweating on the face. However, since the effect was bilateral, it is difficult to draw conclusions from the cold test. The chordotomy did not influence thermoregulatory sweating and hence probably had no effect on the vasomotor responses. The chordotomy on this patient was done by inserting a cataract

knife straight into the cord just anterior to the dentate ligament. The section was about 3 mm. deep and 2.5 mm. wide. The anterior columns and the greater part of the spinothalamic tracts were spared. Motor, bowel, and bladder function and sweating were unimpaired by this procedure. Sensibility to pain and temperature was lost up to a level below the knees. This patient has been reported in another paper.<sup>2</sup>

*Experiment 2.*—December 3, 1939. Margaret B., aged 31, 351 days after removal of the inferior cervical and upper three dorsal ganglia on the left (Table II).

TABLE II  
EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE (° C.) |  |  |                        |      |                       |       |                      |       |        |       |
|-------------------|-------------------------|--|--|------------------------|------|-----------------------|-------|----------------------|-------|--------|-------|
|                   | RIGHT                   | LEFT                                       |  | RIGHT                  | LEFT | RIGHT                 | LEFT  | RIGHT                | LEFT  | RIGHT* | LEFT* |
| Forehead          | 1.0                     | 1.0  |  | -1.5                   | -1.5 | -1.3                  | -3.8  | -1.3                 | -3.8  | -5.3   | -1.8  |
| Cheek             | 1.0                     | 1.0  |  | -2.5                   | -1.5 | -6.8                  | -5.8  | -6.8                 | -5.8  | -7.8   | -6.8  |
| Neck              | 2.0                     | 2.0  |  | -1.0                   | 0.0  | -4.3                  | -4.3  | -4.3                 | -4.3  | -6.3   | -6.3  |
| Chest             | 2.0                     | 2.0  |  | -1.5                   | -1.5 | -5.3                  | -5.3  | -6.3                 | -5.8  | -8.3   | -7.8  |
| Arm               | 1.0                     | 1.5  |  | -1.5                   | -1.5 | -6.3                  | -4.8  | -7.8                 | -6.8  | -8.8   | -8.3  |
| Forearm           | 1.0                     | 1.0  |  | -3.0                   | -2.5 | -6.8                  | -5.8  | -8.8                 | -5.8  | -9.8   | -6.8  |
| Finger            | -2.0                    | 0.0  |  | -8.5                   | -6.5 | (-11.3)               | -11.3 | (-11.3)              | -11.3 | (-9.3) | -11.3 |
| Abdomen           | 2.0                     | 2.0  |  | -3.0                   | -3.0 | -6.3                  | -6.3  | -7.8                 | -7.8  | -9.8   | -9.8  |
| Thigh             | 0.5                     | 1.5  |  | -4.0                   | -1.0 | -7.3                  | -7.3  | -8.3                 | -8.8  | -8.8   | -10.3 |
| Calf              | 0.0                     | 0.0  |  | -5.5                   | -5.0 | -8.3                  | -7.8  | -9.3                 | -8.3  | -9.3   | -8.3  |
| Ankle             | -0.5                    | -0.5                                       |  | -5.0                   | -5.0 | -7.8                  | -8.3  | -9.8                 | -9.8  | -9.3   | -9.3  |
| Mouth temperature | 38.0° C.<br>100.0° F.   |  |  | 38.04° C.<br>100.1° F. |      | 37.60° C.<br>99.7° F. |       | 37.0° C.<br>98.6° F. |       |        |       |
| B. P.             | 116/60                  |  |  | 112/64                 |      | 110/84                |       | 110/84               |       |        |       |
| Pulse rate        | 116                     |  |  | 112                    |      | 116                   |       | 108                  |       |        |       |
| Time (P.M.)       | 2:50                    | 2:59                                       |  | 3:05                   |      | 3:30                  |       | 4:00                 |       |        |       |
| Remarks           | Basal                   | En-<br>ters<br>re-<br>frig-<br>era-<br>tor |  |                        |      |                       |       |                      |       |        |       |

\*Last two columns show differences between first and last readings.

( ) The readings in parentheses should be greater (colder) because instrument needle deflected off the scale.

Room temperature, 24.0° C.; temperature of refrigerator, 0° C.

*Observations and Comment.*—The left (denervated) middle finger was 2° warmer than the right at room temperature. After six minutes in the icebox the left was 6.5° cooler, but was still 2° warmer than the right, the temperature of which had dropped a similar amount. Thereafter, the needle ran off the scale, and accurate readings could not be obtained for the finger. The temperatures of the palms of the hands at the end of the experiment were: right, -10.0; and left, -4.0. Inasmuch as the temperature of the right middle finger deflected the needle off the scale of the instrument, the palm temperatures show more accurately the magnitude of the difference on the two sides. The left arm and left side of the face felt subjectively warm throughout the experiment, whereas the right ached from cold. Shivering did not occur until experiment was nearly completed. At this time, pilomotor activity became evident except in the sympathectomized zone.

*Experiment 3.*—Jan. 31, 1940. Mabel R., aged 23, 377 days after section of posterior roots C 8 to T 4, inclusive, on both sides, and 328 days after removal of the right inferior cervical and upper two dorsal ganglia (Table III).

TABLE III

## EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE (° C.) |      |                       |         |                          |         |                       |         |         |         |
|-------------------|-------------------------|------|-----------------------|---------|--------------------------|---------|-----------------------|---------|---------|---------|
|                   | RIGHT                   | LEFT | RIGHT                 | LEFT    | RIGHT                    | LEFT    | RIGHT                 | LEFT    | RIGHT*  | LEFT*   |
| Forehead          | 2.0                     | 2.0  | -1.7                  | -2.2    | -3.4                     | -2.9    | -3.3                  | -3.3    | -5.3    | -5.3    |
| Cheek             | 2.5                     | 2.0  | -0.7                  | -2.7    | -1.4                     | -6.4    | -2.8                  | -7.8    | -5.3    | -9.8    |
| Nose              | 0                       | -1.0 | -2.2                  | -7.2    | -3.4                     | -7.4    | -5.3                  | -9.8    | -5.3    | -10.8   |
| Ears              | 0                       | -0.5 | -3.7                  | -5.2    | -4.9                     | -7.4    | -5.3                  | -7.8    | -5.3    | -8.3    |
| Neck              | 3.0                     | 3.0  | -0.2                  | -0.2    | -0.9                     | -0.9    | -1.3                  | -1.8    | -4.3    | -4.8    |
| Chest             | 2.0                     | 2.0  | -0.2                  | -0.2    | -0.9                     | -1.4    | -1.3                  | -1.8    | -3.3    | -3.8    |
| Forearm           | 2.5                     | 2.0  | -1.2                  | -2.2    | -3.4                     | -5.4    | -4.3                  | -6.3    | -6.8    | -8.3    |
| Palm              | 2.5                     | 2.5  | -1.7                  | -1.7    | -2.9                     | -2.9    | -3.8                  | -5.3    | -6.3    | -7.8    |
| Thumb             | 1.5                     | -2.0 | -2.2                  | -5.7    | -4.9                     | -7.9    | -6.8                  | -9.3    | -8.8    | -11.3   |
| Finger            | 1.0                     | -7.5 | -5.7                  | (-10.2) | -8.9                     | (-10.9) | (-10.9)               | (-10.9) | (-12.4) | (-17.9) |
|                   |                         |      | -8.7                  | (-10.2) | -10.9                    | (-10.9) | (-10.9)               | (-10.9) | (-11.9) | (-18.4) |
| Mouth temperature | 37.04° C.<br>98.7° F.   |      | 36.88° C.<br>98.4° F. |         | 36.32° C.<br>97.3° F.    |         | 36.77° C.<br>98.2° F. |         |         |         |
| B. P.             | 128/70                  |      | 130/88                |         | 130/84                   |         | 120/70                |         |         |         |
| Pulse rate        | 60                      |      | 76                    |         | 80                       |         | 64                    |         |         |         |
| Time (P.M.)       | 4:15                    |      | 4:35                  |         | 4:45                     |         | 4:55                  |         |         |         |
| Remarks           | Basal                   |      | 4:25                  |         | Enters re-<br>frigerator |         |                       |         |         |         |

\*Last two columns show differences between first and last readings.

( ) The readings in parentheses should be greater (colder) because the needle deflected slightly off the scale.

Room temperature, 22.0° C.; temperature of refrigerator, 6.0° C.



Fig. 1.—The hands of M. R. after being in the refrigerator. The skin of the left (normal) hand is flushed to a much greater degree, and is slightly cyanotic, as compared to the right (sympathectomized) hand.

At the time this photograph was taken the left palm was  $2.5^{\circ}$  C. colder than the right, but, since the temperature of the right palm had dropped  $8.8^{\circ}$  C. in the refrigerator, as compared with a drop of  $11.3^{\circ}$  C. on the left, we do not feel that a terminal difference of  $2.5^{\circ}$  C. could fully account for the marked difference in appearance of the hands.



*Observations and Comment.*—We do not feel that section of the posterior roots from C 8 to T 4 had any demonstrable influence on the response to cooling. The patient exhibited pilomotor activity at 4:30, except in the sympathectomized area. After five minutes in the refrigerator there was a great difference in the appearance of the two hands. The right (denervated) hand did not change in color and felt warm, whereas the left became cold, mottled, and cyanotic. This appearance shaded off up to the elbow (See Fig. 1). Subjectively, the right hand felt warm, but the left fingers stung with cold throughout the experiment. The body felt subjectively warmer at 5:30, and shivering ceased. At the termination of the experiment the right hand became slightly flushed also, but not anything like so much as the left.

*Experiment 4.*—Nov. 25, 1939. Ralph McG., aged 55, 121 days after removal of the inferior cervical and upper six dorsal ganglia on the left (Table IV).

*Observations and Comment.*—At room temperature the temperature of the middle fingers on the two sides was the same. At the end of the experiment, the left (denervated) middle finger was only  $0.5^{\circ}$  warmer than the right; its temperature had dropped  $10.5^{\circ}$ . When the subject entered the refrigerator, a pilomotor reaction was marked over the body except over the sympathectomized zone, and remained so throughout the experiment. At 10:31 he started to shiver. This subsided, but again became extreme at 10:45. He never felt subjectively warm except in the sympathectomized skin zone. The experiment was terminated because the patient was very uncomfortable. His mouth temperature dropped  $1.4^{\circ}$  F.

*Experiment 5.*—Dec. 31, 1939. Marlow S., aged 48, nineteen days after splanchnicotomy and removal of the first, second, and third lumbar ganglia on the right (Table V).

*Observations and Comment.*—He began to feel cold and shivered vigorously in two minutes. At 4:45 he felt warmer and stopped shivering. Pilomotor activity was generalized except over the thigh and leg on the right. At the beginning of the experiment the right (denervated) large toe was  $4^{\circ}$  warmer than the left. At the end of the experiment the temperature of the right toe had dropped  $7.6^{\circ}$ , but it was still more than  $6^{\circ}$  warmer than the left, which was  $9.6^{\circ}$  cooler. The right (denervated) foot and leg felt subjectively warm throughout the experiment.

*Experiment 6.*—Feb. 11, 1940. Eline R., aged 39, 510 days after right-sided splanchnicotomy and removal of the right first and second lumbar ganglia, and 455 days after section of anterior and posterior roots T 1 to T 5, inclusive, on both sides (Table VI).

*Observations and Comment.*—There was marked shivering on entering the refrigerator. At 4:08, pilomotor activity was generalized in the usual areas, except over the right leg. At 4:17, shivering stopped. Throughout the experiment the left foot was definitely more red and dusky than the right. At the beginning of the experiment the right (denervated) large toe was  $4.5^{\circ}$  warmer than the left. At the end of the experiment the temperature of the right toe had dropped  $12.5^{\circ}$ , but it was still more than  $3^{\circ}$  warmer than the left, which had become  $11.0^{\circ}$  cooler. The right foot and leg felt subjectively warm throughout the experiment.

*Experiment 7.*—Jan. 1, 1940. Richard W., aged 29, 411 days after removal of the second, third, and fourth lumbar ganglia on both sides (Table VII).

*Observations and Comment.*—This patient was admitted because of intermittent claudication, and biopsy of a vessel of the leg ultimately proved that he had

TABLE IV  
EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE (° C.) |                              |                       |                       |                       |                       |                       |                       |                       |                       |                       |                       |
|-------------------|-------------------------|------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                   | RIGHT                   | LEFT                         | RIGHT                 | LEFT                  | RIGHT                 | LEFT                  | RIGHT                 | LEFT                  | RIGHT                 | LEFT                  | RIGHT*                | LEFT*                 |
| Forehead          | 1.5                     | 1.5                          | -2.4                  | -1.9                  | -3.4                  | -1.9                  | -2.9                  | -2.9                  | -4.0                  | -2.5                  | -5.5                  | -4.0                  |
| Cheek             | 0                       | 0                            | -1.9                  | -1.9                  | -5.9                  | -3.9                  | -4.9                  | -4.9                  | -6.5                  | -6.0                  | -6.5                  | -6.0                  |
| Neck              | 1.5                     | 2.0                          | -0.4                  | -0.4                  | -3.4                  | -1.4                  | -2.4                  | -2.4                  | -4.0                  | -2.0                  | -5.5                  | -4.0                  |
| Chest             | 1.5                     | 1.5                          | -0.4                  | -0.4                  | -2.9                  | -1.9                  | -2.9                  | -2.9                  | -3.5                  | -3.5                  | -5.0                  | -5.0                  |
| Arm               | 1.5                     | 1.5                          | -0.9                  | -1.9                  | -4.4                  | -2.4                  | -4.9                  | -4.9                  | -4.5                  | -4.5                  | -6.0                  | -6.0                  |
| Forearm           | 1.0                     | 1.0                          | -1.4                  | -1.4                  | -3.4                  | -2.4                  | -3.4                  | -3.4                  | -4.0                  | -4.0                  | -5.0                  | -5.0                  |
| Finger            | 0                       | 0                            | -5.9                  | -4.9                  | -10.9                 | -8.4                  | -10.4                 | -10.4                 | -11.0                 | -10.5                 | -11.0                 | -10.5                 |
| Abdomen           | 1.5                     | 1.5                          | -0.4                  | -0.4                  | -3.4                  | -1.9                  | -3.4                  | -3.4                  | -3.0                  | -3.0                  | -4.5                  | -4.5                  |
| Thigh             | 0.5                     | 0.5                          | -2.4                  | -2.4                  | -3.4                  | -2.4                  | -3.4                  | -3.4                  | -3.0                  | -3.5                  | -4.0                  | -4.0                  |
| Calf              | -0.5                    | -0.5                         | -1.9                  | -1.9                  | -3.9                  | -2.4                  | -3.9                  | -3.9                  | -4.5                  | -4.5                  | -4.0                  | -4.0                  |
| Ankle             | -1.0                    | -1.0                         | -4.4                  | -4.4                  | -7.4                  | -6.4                  | -7.4                  | -7.4                  | -7.0                  | -8.0                  | -6.0                  | -7.0                  |
| Mouth temperature | 36.66° C.<br>98.0° F.   | 36.55° C.<br>97.8° F.        | 36.06° C.<br>96.9° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. | 35.90° C.<br>96.6° F. |
| B. P.             | 96/70                   | 110/72                       | 104                   | 104                   | 114/76                | 114/76                | 114/76                | 114/76                | 114/76                | 114/76                | 114/76                | 114/76                |
| Pulse rate        | 90                      | 108                          | 104                   | 104                   | 112                   | 112                   | 112                   | 112                   | 112                   | 112                   | 112                   | 112                   |
| Time              | 10:20                   | 10:27                        | 10:35                 | 10:35                 | 10:45                 | 10:45                 | 10:45                 | 10:45                 | 10:55                 | 10:55                 | 10:55                 | 10:55                 |
| Remarks           | Basal                   | 10:25<br>Enters refrigerator | 10:35                 | 10:35                 | 10:45                 | 10:45                 | 10:45                 | 10:45                 | 10:55                 | 10:55                 | 10:55                 | 10:55                 |

\*Last two columns show differences between first and last readings.  
Room temperature, 27.7° C.; temperature of refrigerator, 0.5° C.

TABLE V

## EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE (° C.) |      |                             |      |                      |         |                       |         |       |        |       |        |
|-------------------|-------------------------|------|-----------------------------|------|----------------------|---------|-----------------------|---------|-------|--------|-------|--------|
|                   | RIGHT                   | LEFT | RIGHT                       | LEFT | RIGHT                | LEFT    | RIGHT                 | LEFT    | RIGHT | LEFT   | RIGHT | LEFT   |
| Forehead          | 2.0                     | 2.0  | -0.3                        | -0.3 | -2.4                 | -1.4    | -3.6                  | -3.1    | -5.6  | -5.1   | -5.6  | -5.1   |
| Cheek             | 2.0                     | 1.0  | -2.8                        | -3.8 | -5.9                 | -5.9    | -5.6                  | -6.1    | -7.6  | -7.1   | -7.6  | -7.1   |
| Neck              | 3.0                     | 2.5  | -1.8                        | -0.8 | -3.4                 | -2.4    | -2.6                  | -2.6    | -5.6  | -5.1   | -5.6  | -5.1   |
| Chest             | 2.0                     | 2.0  | -1.8                        | -1.8 | -3.9                 | -3.9    | -5.1                  | -5.1    | -7.1  | -7.1   | -7.1  | -7.1   |
| Arm               | 1.0                     | 1.0  | -2.3                        | -2.8 | -4.4                 | -4.4    | -5.6                  | -5.6    | -6.6  | -6.6   | -6.6  | -6.6   |
| Forearm           | 0.5                     | 1.0  | -2.8                        | -1.8 | -4.4                 | -3.4    | -4.6                  | -4.6    | -5.1  | -5.6   | -5.1  | -5.6   |
| Palm              | 0.5                     | 1.0  | -2.8                        | -2.3 | -3.9                 | -3.4    | -5.6                  | -6.1    | -7.1  | -7.1   | -7.1  | -7.1   |
| Finger            | -2.0                    | -1.5 | -8.3                        | -5.3 | -8.4                 | -8.4    | -9.6                  | -10.6   | -7.6  | -12.1  | -7.6  | -12.1  |
| Abdomen           | 1.5                     | 1.5  | -2.3                        | -2.3 | -3.9                 | -3.9    | -4.6                  | -4.6    | -6.6  | -6.6   | -6.6  | -6.6   |
| Thigh             | 2.0                     | 1.5  | -1.3                        | -1.8 | -2.9                 | -3.9    | -4.1                  | -4.6    | -6.1  | -6.1   | -6.1  | -6.1   |
| Calf              | 1.5                     | 1.5  | -1.8                        | -1.8 | -4.4                 | -4.4    | -5.1                  | -5.1    | -6.6  | -6.6   | -6.6  | -6.6   |
| Ankle             | 2.0                     | 1.0  | -2.8                        | -3.3 | -4.4                 | -5.4    | -4.6                  | -6.6    | -6.6  | -7.6   | -6.6  | -7.6   |
| Toe               | 3.0                     | -1.0 | -4.3                        | -8.8 | -4.9                 | (-10.4) | -4.6                  | (-10.6) | -7.6  | (-9.6) | -7.6  | (-9.6) |
| Mouth temperature | 37.0° C.<br>98.6° F.    |      | 35.75° C.<br>96.4° F.       |      | 36.5° C.<br>97.7° F. |         | 36.10° C.<br>97.0° F. |         |       |        |       |        |
| B. P.             | 194/150                 |      | 206/150                     |      | 220/164              |         | 200/150               |         |       |        |       |        |
| Pulse rate        | 100                     |      | 120                         |      | 124                  |         | 120                   |         |       |        |       |        |
| Time              | 4:20 (P.M.)             |      | 4:35                        |      | 4:45                 |         | 4:55                  |         |       |        |       |        |
| Remarks           | Basal                   |      | 4:30<br>Enters refrigerator |      | 4:45                 |         | 4:55                  |         |       |        |       |        |

\*Last two columns show differences between first and last readings.

( ) The readings in parentheses should be greater (colder) because the needle of the instrument deflected somewhat off the scale.

Room temperature, 22.0° C.; temperature of refrigerator, 5.0° C.



TABLE VI  
EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE (° C.)          |      |                                  |                     |                                  |         |                                  |         |                                  |         |         |         |
|-------------------|----------------------------------|------|----------------------------------|---------------------|----------------------------------|---------|----------------------------------|---------|----------------------------------|---------|---------|---------|
|                   | RIGHT                            | LEFT | RIGHT                            | LEFT                | RIGHT                            | LEFT    | RIGHT                            | LEFT    | RIGHT                            | LEFT    | RIGHT*  | LEFT*   |
| Forehead          | 4.0                              | 4.0  | -1.5                             | -1.5                | -2.0                             | -2.0    | -4.2                             | -3.7    | -4.5                             | -3.5    | -8.5    | -7.5    |
| Cheek             | 3.5                              | 3.5  | -2.5                             | -2.5                | -5.0                             | -5.5    | -6.2                             | -7.2    | -5.5                             | -6.5    | -9.0    | -10.0   |
| Nose              | 1.5                              | 2.0  | -6.0                             | -5.5                | -8.0                             | -8.0    | -9.2                             | -8.7    | -8.5                             | -8.5    | -10.0   | -10.5   |
| Ears              | 3.0                              | 3.0  | -4.5                             | -3.5                | -6.5                             | -6.5    | -7.7                             | -8.2    | -8.5                             | -8.0    | -11.5   | -11.0   |
| Neck              | 4.0                              | 4.0  | -0.5                             | -1.0                | -3.0                             | -3.0    | -3.7                             | -3.7    | -4.0                             | -4.0    | -8.0    | -8.0    |
| Chest             | 4.0                              | 4.0  | -2.0                             | -1.5                | -4.0                             | -4.0    | -5.2                             | -4.7    | -5.0                             | -5.0    | -9.0    | -9.0    |
| Arm               | 3.0                              | 3.0  | -1.0                             | -1.5                | -5.0                             | -5.0    | -5.7                             | -5.7    | -6.0                             | -6.0    | -9.0    | -9.0    |
| Forearm           | 3.0                              | 2.0  | -3.5                             | -3.5                | -6.0                             | -6.0    | -6.7                             | -7.2    | -7.0                             | -7.0    | -10.0   | -9.0    |
| Palm              | 1.5                              | 0.5  | -3.0                             | -3.5                | -6.0                             | -6.5    | -7.2                             | -9.2    | -7.5                             | -8.5    | -9.0    | -9.0    |
| Thumb             | -0.5                             | -1.5 | -8.0                             | -10.0               | (-11.0)                          | (-11.0) | (-11.2)                          | (-11.2) | (-11.5)                          | (-11.5) | (-11.0) | (-11.0) |
| Finger            | -2.5                             | -3.0 | -10.0                            | (-10.5)             | (-11.0)                          | (-11.0) | (-11.2)                          | (-11.2) | (-11.5)                          | (-11.5) | (-9.0)  | (-8.5)  |
| Abdomen           | 2.5                              | 3.0  | -4.5                             | -3.5                | -7.0                             | -6.0    | -7.7                             | -7.2    | -8.0                             | -7.5    | -10.5   | -10.5   |
| Thigh             | 2.5                              | 2.5  | -3.0                             | -3.5                | -6.0                             | -6.5    | -6.7                             | -7.2    | -7.0                             | -7.5    | -9.5    | -9.5    |
| Calf              | 3.0                              | 3.0  | -4.0                             | -4.0                | -7.0                             | -7.0    | -8.7                             | -8.2    | -7.5                             | -6.5    | -10.5   | -9.5    |
| Ankle             | 3.0                              | 1.0  | -4.0                             | -5.0                | -5.5                             | -7.5    | -6.2                             | -8.2    | -6.5                             | -8.5    | -9.5    | -9.5    |
| Foot              | 3.5                              | 2.5  | -3.0                             | -3.5                | -3.0                             | -6.5    | -6.2                             | -8.2    | -6.0                             | -8.5    | -9.5    | -11.0   |
| Large toe         | 4.0                              | -0.5 | -2.5                             | -6.5                | -5.5                             | -11.0   | -7.2                             | (-11.2) | -8.5                             | (-11.5) | -12.5   | (-11.0) |
| Small toe         | 3.0                              | -1.5 | -5.5                             | -8.0                | (-11.0)                          | (-11.0) | (-11.2)                          | (-11.2) | (-11.5)                          | (-11.5) | (-14.5) | (-12.5) |
| Mouth temperature | 37.08° C.<br>98.8° F.<br>190/136 |      | 37.56° C.<br>99.6° F.<br>240/142 |                     | 37.30° C.<br>99.2° F.<br>218/118 |         | 37.30° C.<br>99.2° F.<br>190/136 |         | 37.30° C.<br>99.2° F.<br>194/116 |         |         |         |
| B. P.             |                                  |      |                                  |                     |                                  |         |                                  |         |                                  |         |         |         |
| Pulse rate        |                                  |      |                                  |                     |                                  |         |                                  |         |                                  |         |         |         |
| Time (P.M.)       |                                  |      |                                  |                     |                                  |         |                                  |         |                                  |         |         |         |
| Remarks           | Basal                            | 4:01 | 4:10                             | Enters refrigerator | 76                               | 4:30    | 80                               | 4:40    | 76                               | 4:50    |         |         |

\*Last two columns show differences between first and last readings.

( ) The figures in parentheses should be greater (colder) because the instrument needle deflected off the scale.  
Room temperature, 22.4° C.; temperature of refrigerator, 4.0° C.

TABLE VII  
EFFECT OF LOW TEMPERATURE ON SKIN

| PART              | SKIN TEMPERATURE (° C.) |      |                             |                       |                       |                       |                       |                       |                       |                       |         |         |
|-------------------|-------------------------|------|-----------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|---------|---------|
|                   | RIGHT                   | LEFT | RIGHT                       | LEFT                  | RIGHT                 | LEFT                  | RIGHT                 | LEFT                  | RIGHT                 | LEFT                  | RIGHT*  | LEFT*   |
| Forehead          | 3.0                     | 3.0  | -2.6                        | -2.1                  | -5.0                  | -4.5                  | -4.5                  | -3.5                  | -4.0                  | -3.5                  | -7.0    | -7.5    |
| Cheek             | 3.0                     | 3.0  | -3.1                        | -4.1                  | -5.0                  | -5.0                  | -5.5                  | -6.5                  | -6.0                  | -6.5                  | -9.0    | -9.5    |
| Neck              | 3.0                     | 3.0  | -4.1                        | -3.1                  | -4.0                  | -3.5                  | -4.0                  | -4.5                  | -4.0                  | -4.0                  | -6.5    | -7.0    |
| Chest             | 2.0                     | 2.0  | -5.1                        | -4.1                  | -5.0                  | -5.0                  | -5.5                  | -5.5                  | -6.5                  | -5.5                  | -8.5    | -7.5    |
| Arm               | 2.5                     | 2.5  | -4.1                        | -3.6                  | -5.0                  | -5.0                  | -5.5                  | -6.0                  | -6.0                  | -6.0                  | -8.5    | -8.5    |
| Forearm           | 2.0                     | 2.0  | -3.6                        | -2.6                  | -4.0                  | -4.5                  | -5.0                  | -4.5                  | -4.5                  | -4.5                  | -6.5    | -6.5    |
| Palm              | 1.0                     | 1.0  | -5.1                        | -4.6                  | -6.5                  | -6.0                  | -8.0                  | -8.5                  | -8.5                  | -9.0                  | -9.5    | -10.0   |
| Finger            | 0.5                     | -2.0 | -10.1                       | (-10.6)               | (-11.0)               | (-11.0)               | (-11.5)               | (-11.5)               | (-12.0)               | (-12.0)               | (-12.5) | (-10.0) |
| Abdomen           | 3.0                     | 3.5  | -3.6                        | -3.1                  | -4.0                  | -3.5                  | -5.5                  | -4.5                  | -4.5                  | -4.5                  | -7.5    | -7.5    |
| Thigh             | 1.0                     | 1.5  | -3.6                        | -3.1                  | -4.5                  | -4.0                  | -4.5                  | -5.0                  | -4.5                  | -5.0                  | -5.5    | -6.5    |
| Calf              | 2.5                     | 2.0  | -3.6                        | -4.1                  | -5.0                  | -5.5                  | -5.5                  | -6.0                  | -5.5                  | -5.5                  | -8.0    | -7.5    |
| Ankle             | 2.5                     | 2.5  | -4.6                        | -4.6                  | -6.0                  | -6.5                  | -6.5                  | -7.0                  | -7.0                  | -7.0                  | -9.5    | -9.5    |
| Toe               | 3.0                     | 3.0  | -4.6                        | -4.6                  | -5.5                  | -5.0                  | -6.5                  | -6.0                  | -7.0                  | -6.5                  | -10.0   | -9.5    |
| Mouth temperature | 36.88° C.<br>98.4° F.   |      | 36.10° C.<br>97.0° F.       | 36.10° C.<br>97.0° F. | 36.10° C.<br>97.0° F. | 36.10° C.<br>97.0° F. | 36.10° C.<br>97.0° F. | 36.10° C.<br>97.0° F. | 36.10° C.<br>97.0° F. | 36.10° C.<br>97.0° F. |         |         |
| B. P.             | 130/100                 |      | 140/105                     | 140/105               | 160/110               | 160/110               | 144/110               | 136/100               | 136/100               | 136/100               |         |         |
| Pulse rate        | 96                      |      | 92                          | 84                    | 88                    | 88                    | 88                    | 88                    | 88                    | 88                    |         |         |
| Time (P.M.)       | 1:45                    |      | 2:05                        | 2:15                  | 2:30                  | 2:30                  | 2:30                  | 2:40                  | 2:40                  | 2:40                  |         |         |
| Remarks           | Basal                   |      | 1:55<br>Enters refrigerator | 2:05<br>tor           |                       |                       |                       |                       |                       |                       |         |         |

\*Last two columns show differences between first and last readings.

( ) The figures in parentheses should be greater (colder) because the instrument needle deflected off the scale.  
Room temperature, 22.0° C.; temperature of refrigerator, 4.0° C.

Buerger's disease, although there were no trophic changes. The temperatures of the large toes were equal at the beginning of the experiment, and only  $0.5^{\circ}$  different at the end; that of the right had dropped  $10^{\circ}$ . His feet felt subjectively warm throughout the experiment, "like they were in an oven," but his hands ached with cold and felt frozen. His toes were warmer than his fingers at room temperature.\*

He felt cold on entering the refrigerator, and his legs shivered some. At 2:05 there was general shivering, and pilomotor activity was generalized except over the legs and feet. At 2:15 he stopped shivering and felt warmer. At 2:30 he started shivering again.

#### DISCUSSION

*Influence of Sympathectomy on Response of Arterioles to Cold.*—Several outstanding facts are demonstrated by these experiments. When the nude subject is exposed to an environment of  $0^{\circ}$  to  $5^{\circ}$  C., the temperature of the skin falls rapidly. The hands, fingers, feet, and toes show the greatest fall ( $10^{\circ}$  to  $18^{\circ}$ ). The temperature of a sympathectomized finger or toe may drop  $10^{\circ}$  or  $15^{\circ}$ , but, in all except one patient, the finger remained  $3^{\circ}$  to  $6^{\circ}$  warmer than its normal mate.† This patient (Ralph McG., Experiment 4) was the only one in the group the temperature of whose fingers was not materially changed by cervicodorsal ganglionectomy. In his case, at the end of the cold test the fingers on the two sides had cooled to practically the same degree. We have pointed out in a previous publication<sup>1</sup> that, in our experience, the central sympathetic vasomotor control of the hands and fingers diminishes with age, and, in persons past 50 without vasospastic disease, we have usually found little or no change in finger temperature after cervicodorsal ganglionectomy. After unilateral cervicodorsal ganglionectomy which was recently done on two elderly patients, a man of 67 and a woman of 80, the sympathectomized fingers did not become warmer. In our experience, the toes have always become warmer after lumbar ganglionectomy, regardless of age.

The refrigerator experiment demonstrates the magnitude of the reaction of the vessels (arterioles) themselves to cold (first order reaction).‡ No doubt, if the extremities of these patients had remained outside the refrigerator and had been independently exposed to room temperature, the sympathectomized hand or foot would not have changed its tempera-

\*Sixteen suitable persons were exposed to room temperature in the nude for thirty minutes. The skin temperatures of the large toes and middle fingers of each were taken. The large toe was colder than the middle finger in every case. The averages were as follows:

|               | RIGHT | LEFT |
|---------------|-------|------|
| Large toe     | 4.0   | 3.8  |
| Middle finger | 7.6   | 7.6  |

Hence, the toes in these subjects were  $3.6^{\circ}$  to  $3.8^{\circ}$  colder than the fingers. This offers some basis for comparison.

†These results are in keeping with those of Lewis and Landis.<sup>3</sup>

‡We refer to the response of the vessel itself, without central connections, as a reaction of the first order. A response contingent upon reflexes through the cord is a reaction of the second order. A response contingent upon impulses from the hypothalamus is a reaction of the third order.

ture substantially, but, in our experiments, the part itself was exposed to the same temperature as the remainder of the body. In a recent report<sup>1</sup> we emphasized this point in relation to the heat test, and in comparing our results with those of Lewis and Pickering.<sup>4</sup>

In the refrigerator experiment we are measuring on the sympathectomized side the capacity of the denervated arterioles to respond to cold, whereas, on the normal side, we are measuring the same thing plus a superimposed vasoconstriction due to activity of the central (third order) (and second order?) mechanisms. The magnitude of the *first order* reaction is remarkable.

Thus we have a quantitative method of ascertaining the magnitude of the role played by the central vasomotor governor when the body is exposed to severe cold. The mechanism is more active in young persons, and may be entirely absent in the hands of aged persons. This is probably one of the reasons why heat conservation becomes less adequate with age.

In young persons the mouth temperature usually drops  $1^{\circ}$  or  $2^{\circ}$  after five or ten minutes in the refrigerator. At this time there is a subjective feeling of cold. Shivering\* occurs for five or ten minutes, and then may cease, after which the mouth temperature begins to rise and the patient has a subjective feeling of warmth.

*Influence of Sympathectomy on Pain Incident to Cold.*—Although the sympathectomized side objectively becomes quite cold in the refrigerator, the patient has the feeling that it is "warm as toast," as compared to the normal side, which aches and stings with cold. This is true of not only the digits, but also of the entire sympathectomized zone. When our subjects were exposed in the refrigerator the normal hand shortly began to sting and ache, and subjectively was decidedly cold. In no case did these sensations occur in the sympathectomized hand or foot. In all of our subjects the sympathectomized hand felt comfortable and devoid of pain, even at a time when it was objectively as cold or colder than was the normal hand, which had begun to sting and ache. Under the conditions of these experiments, when only a unilateral cervicodorsal gangliotectomy has been done, we are forced to conclude that the pain incident to cold is materially influenced by the sympathetic system. Whether this type of pain is mediated by afferent sympathetic fibers or whether the elimination of efferent sympathetic fibers raises the threshold of somatic stimulability is debatable, and remains to be proved. Vasoconstriction undoubtedly initiates the pain impulses in question.

\*We had occasion to test one patient who had had a bilateral chordotomy at C 8. The ependymal knife had been inserted about 1 to 2 mm. anterior to the dentate ligament, and was brought out at the anterior median fissure, thus interrupting the spinothalamic tracts and anterior columns. This patient shivered most vigorously above the nipples. There was not a solitary shiver below this level. The phenomenon was so definite that there can be no question that the neural mechanism for shivering had been interrupted. His pyramidal tracts were intact. Sweating and control of the bowels and bladder were unimpaired. There was loss of sensibility for pain and temperature below the nipples.

We have had some patients with unilateral cervicodorsal ganglionectomy clutch a block of ice in each hand. We used blocks one-half the size of an ordinary refrigerator ice cube. One patient (Margaret B., Experiment 2) was compelled to drop the ice from the normal hand in twenty seconds, but she retained the ice in the sympathectomized hand, without discomfort, until it melted. Another patient was compelled, because of pain, to drop the ice from the normal hand in fifteen seconds, but retained the ice in the sympathectomized hand, without discomfort, for two minutes. In these cases there was no demonstrable diminution in the normal ability to discriminate differences in temperature on the sympathectomized side. The ability to discriminate differences and changes in temperature is a function of somatic afferent nerves. Only pain which is incident to vasoconstriction is modified in some way by the sympathetic system. When the patient compares the sensation from a sympathectomized skin zone to that from a normal zone, and when both are subjected to the same cold environment, the sensations of temperature are distinctly different. Subjectively, the sympathectomized zone feels much warmer.

Richard W. (Experiment 7) had Buerger's disease, with intermittent claudication. He had had a bilateral lumbar ganglionectomy. When in the refrigerator he stated that his feet felt as if they were in an oven, while his hands ached and felt frozen. The same reasoning already given concerning the mediation of pain from vasoconstriction in the upper extremities applies to the lower extremities also.

We have recently made more detailed studies concerning the influence of the sympathetics on pain incident to cold, and on the comparative interpretation of temperature.<sup>5</sup> The benefit derived from sympathectomy in the treatment of Raynaud's disease can undoubtedly be attributed, in part, to elimination of the pain of vasoconstriction herein described. Further evidence in support of this statement has been obtained and will be submitted for publication.

*Influence of the Sympathetics on Capillary Dilatation in the Hands Caused by Exposure of the Entire Body to Cold.*—At the end of a refrigerator experiment a sympathectomized hand or foot will, at most, have become only slightly flushed (first order capillary dilatation). The normal hand, however, becomes flushed early, and later may present a dusky, slightly cyanotic hue. This capillary dilatation probably serves to protect the skin, and is largely under the control of the central mechanism. The late cyanotic hue is due to the great retardation in the velocity of capillary blood caused by arteriolar constriction. Capillary dilatation following the stimulus of cold is partly a peripheral (first order) response and partly a central (third order) (and second order?) response, and is normally, a combination of the three. After unilateral cervicodorsal ganglionectomy, a small block of ice on the forearm or hand will produce the same phenomenon, and to the same degree, on the nor-

mal and sympathectomized sides. The first effect is pallor. This is followed shortly by reddening limited to the area of application. When the ice is removed, the flush persists for some time. This is a local (first order) reaction. If the patient is taken into a refrigerator ( $0^{\circ}$  to  $5^{\circ}$  C.), so that the entire body is exposed to cold, the first order reaction will be markedly re-enforced in the normal hand.\* The normal hand will become quite flushed, and later may present a cyanotic hue, but the sympathectomized hand will become only slightly flushed (see Fig. 1).

The flushing after local application of cold which was studied by Lewis<sup>6</sup> is a local reaction of the first order. His supplementary studies<sup>7</sup> would involve first (and second?) and third order responses. Lewis found that the local reaction did not occur, as is also true of the histamine flare, after degeneration of peripheral nerves. The reaction was not abolished by degeneration of sympathetic nerves only. Lewis therefore attributed the reaction to an axon reflex. Inasmuch as this first order response is not influenced by degeneration of sympathetic nerves, we must have witnessed the first order response in the sympathectomized hand in pure form, and as a local response to cold. The increased and marked capillary dilatation in the normal hand in response to severe cold is strong comparative evidence that there is a central control of capillary dilatation.

Cold did not cause the unilateral flushing of the face which was brought about by exposure to heat.<sup>1</sup> In the refrigerator the phenomenon was limited to the hands.

*A Dual Mechanism of Capillary Responses.*—We have presented evidence that there is a central control of capillary dilatation in response to both extreme heat<sup>1</sup> and severe cold. The control is mediated through the thoracolumbar sympathetic system. This control is abolished by sympathectomy, but there still remains a local (first order) response.† Lewis<sup>6</sup> has shown that this local response is not abolished by degeneration of sympathetic fibers, but is abolished by degeneration of somatic sensory nerves. The first order response appears to be comparable in all respects to the histamine flare, and hence must be governed by an axon reflex mechanism. Therefore, it may well be that the first order mechanism to which we have referred is governed by an axon reflex, and hence is related to the somatic sensory nerves. That mechanism is distinctly different from the one related to the sympathetic system.

Skin arterioles are controlled by at least a dual mechanism, peripheral and central. We shall disregard for the present any possible role that reflexes through the spinal cord may play.‡ The peripheral mechanism

\*In the refrigerator the normal hand becomes objectively colder than the sympathectomized hand, in spite of the greater capillary flushing.

†By first order response we do not imply that the vessel in question is necessarily devoid of nerve fibers, but only that it is devoid of central connections.

‡To obtain conclusive evidence that there are cord reflexes (second order mechanism), we feel that one should carry out studies on the spinal animal or spinal man. Sahs and Fulton<sup>8</sup> have adduced definite evidence of this reflex in spinal monkeys.

of dilatation or constriction of arterioles is contingent upon an inherent reactivity to changes in temperature.\* This reactivity is of great importance and of considerable magnitude when compared to the effects of the central (hypothalamic) mechanism. The peripheral, or first order, mechanism is not an integrated one, but reacts quickly to changes in temperature without requiring a change in the temperature of the blood which circulates through the hypothalamus. Hence, if only a portion of the skin surface is exposed to cold, there is a local adjustment of vessel caliber to meet the issue, exclusive of central reflexes. On the other hand, if the change in environmental temperature or the area of skin exposed is sufficient to warm or cool the blood which circulates through the hypothalamus, the central, or third order, mechanism will function, and will utilize the entire skin surface as an integrated unit in the endeavor to restore and maintain a constant, normal, central temperature. The central mechanism also has other means at its disposal, aside from vasomotor control, i.e., sudomotor and pilomotor activity and shivering.

Sudomotor, vasomotor, and pilomotor activity and shivering vary in their relative magnitudes from person to person and with age. If we take the temperature range from 0° to 48° C., at any given temperature in this range the degree of vasoconstriction in the skin of the fingers will depend on the tone inherent in the vessel, plus the degree of vasoconstriction imposed by the sympathetic mechanism. At 35.5° C. (96° F.), which is ordinarily regarded as room temperature, the magnitude of this latter factor will vary with different persons and with age. We believe that it is usually greater for the toes than for the fingers.

We have found that, after a unilateral cervicodorsal ganglionectomy, the difference in temperature of the fingers on the two sides will vary from time to time, even when the nude body is always exposed to the same environmental temperature. We have found that this difference varies from 0° to 6° or 7° C.; it is probably contingent upon variations in the psychic and physiologic state that the organism normally undergoes. The psychologic reactions to pain incident to a hypodermic injection or the insertion of a needle into a vein may cause definite changes in the skin temperature of the normal hand.

It is a strange fact that both peripheral and central vascular responses are outstandingly greater for the skin of the carpal and pedal extremities and digits than for the remainder of the skin of the body of man. We believe that this phenomenon is more of physiologic and evolutionary,

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\*Ascroft<sup>9</sup> performed some interesting experiments on monkeys after unilateral cervicodorsal ganglionectomy. The monkeys were placed in a cabinet the temperature of which was kept constant, or so adjusted as to attempt to keep the rectal temperature constant. The hands were outside the cabinet and the outside temperature was changed. Ascroft concluded that after degeneration occurred following cervicodorsal ganglionectomy, the response was much greater to cold than after preganglionic sympathectomy, and hence, after degeneration, the vessels of the skin acquire a greater restoration of inherent tone. If this be consistently true, this factor for the upper extremities would have to be given an importance at least equal to that of circulating adrenaline. We found in our refrigerator experiments, however, that the fall in the temperature of the sympathectomized toes of man (preganglionic) was of the same magnitude as that of the fingers after degeneration (postganglionic) had occurred. These results would not bear out Ascroft's hypothesis.

than of anatomic significance. Judging from our experience, the vessels of the ear of man are not comparable to those of the ear of the rabbit in their response to sympathectomy. For example, we have found little or no difference in the temperature of the two ears of man after unilateral cervicodorsal ganglionectomy, whereas, in the rabbit, vasodilatation of the sympathectomized ear is marked.

Both the systolic and diastolic blood pressures were somewhat elevated during the experiment, and substantially so in the two cases of hypertension (Experiments 1 and 6). There was usually a moderate increase in pulse rate.

### CONCLUSIONS

1. If a nude subject goes from a room at ordinary temperature to one at 0° to 5° C., the skin temperature will drop markedly and rapidly; the hands, fingers, feet, and toes exhibit the most marked change.

2. The central temperature may fall 1° or 2°, followed by shivering. In a young person the central temperature may rise again, shivering will cease for a time, and he will have a subjective feeling of warmth.

3. If one extremity is sympathectomized, exposure in a refrigerator provides a quantitative measure of the peripheral (first order) response to cold on the denervated side, and of the central (third order) (and second order?) response to cold, in addition to the peripheral response, on the normal side.

4. A hand that becomes warmer after cervicodorsal ganglionectomy will remain substantially warmer than its normal mate in a cold environment, although both show evidence of marked arteriolar constriction.

5. A hand that does not become warmer after cervicodorsal ganglionectomy (usually persons over 50) will exhibit the same fall in temperature as its mate in a cold environment, and the temperatures of the hands and fingers will remain equal.

6. Capillary dilatation in response to cold is partly under central control and is probably a protective mechanism.

7. Evidence was obtained which indicates that the pain incident to cold (vasoconstriction) is markedly reduced by sympathectomy. We do not feel that the vasodilatation usually incident to sympathectomy adequately or fully accounts for the altered sensation.

8. The results of the refrigerator experiments indicate the importance and magnitude of the peripheral (first order) vascular response to changes in temperature. They further suggest that the central (third order) mechanism is of importance in extreme changes and in the utilization of the entire skin surface as an integrated unit for heat conservation.

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## AN ELECTROCARDIOGRAPHIC STUDY OF THE EFFECTS OF BOXING

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THE etiologiical relationship of organic heart disease to nonpenetrating trauma of the chest wall is of considerable present-day interest. Although there is no question as to the effect of trauma on the heart in animals, as shown by the work of Kahn and Kahn,<sup>1</sup> Beek,<sup>2</sup> Kissane,<sup>3</sup> and others,<sup>4</sup> no comparable electrocardiographic study in man has been reported, except in a few cases of accidental trauma.

Because there are severe chest blows in strenuous bouts of boxing, it was thought that electrocardiographic study before and after such bouts might indicate evidence of organic damage of the heart. Through the courtesy of the *New York Daily News*, Dr. Irving S. Cutter, and Dr. Henry Blum, we were able to study a group of boys in the annual Golden Gloves Boxing Tournament.

Electrocardiograms of thirty-five boys in the weight classes from 112 pounds to heavyweight were taken before and after each bout. Each match consisted of three rounds of two minutes each, unless stopped sooner by a knockout. All electrocardiograms were taken shortly before and as soon after each bout as was possible and when the subject was in the sitting position. A Cambridge "Simpli-trol" portable string galvanometer was used in each case. Three standard leads and three chest leads were recorded before and after each contestant's bout. The chest leads were CF<sub>1</sub>, CF<sub>2</sub>, and CF<sub>3</sub>, according to the nomenclature recommended by the American Heart Association.<sup>5</sup>

These boys, whose ages ranged from 16 to 24 years, had previously had one or more negative physical examinations, and most of them were in fair condition, although a few were noticeably in poor shape as far as training was concerned. These matches are well known for the keen competition and fast fighting, and many knockouts occurred. Unfortunately, we did not have the opportunity to do complete cardiac examinations on these boys, nor were we able to make a follow-up study at a later date.

Table I gives the average values of the electrocardiographic deflections in the thirty-five cases. In the standard leads 1 millivolt was represented by a string deflection of 1 cm., and, in the precordial leads, by a deflection of 0.5 cm.

*Rate.*—Before the bouts the average heart rate was 81 beats per minute; there were one case of bradycardia (50 beats per minute) and three of tachycardia (105, 108, and 110 beats per minute). In every

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TABLE I

|                   | BEFORE EXERCISE  |                  |               | AFTER EXERCISE   |                  |               |
|-------------------|------------------|------------------|---------------|------------------|------------------|---------------|
|                   | MINIMUM<br>(MM.) | MAXIMUM<br>(MM.) | MEAN<br>(MM.) | MINIMUM<br>(MM.) | MAXIMUM<br>(MM.) | MEAN<br>(MM.) |
| P <sub>1</sub>    | 0                | 2                | 0.79          | 0                | 1.5              | 0.78          |
| P <sub>2</sub>    | 1                | 3                | 1.6           | 1                | 4                | 2.3           |
| P <sub>3</sub>    | 0                | 2.5              | 0.96          | 0                | 3.5              | 1.6           |
| Q <sub>1</sub>    | 0                | 1.5              | 0.13          | 0                | 1                | 0.06          |
| Q <sub>2</sub>    | 0                | 2                | 0.26          | 0                | 4                | 0.59          |
| Q <sub>3</sub>    | 0                | 7                | 0.84          | 0                | 7                | 1.1           |
| Q-CF <sub>1</sub> | 0                | 2                | Only 1 case   | 0                | 5                | Only 1 case   |
| Q-CF <sub>2</sub> | 0                | 12               | Only 1 case   | 0                | 10               | Only 1 case   |
| Q-CF <sub>4</sub> | 0                | 1                | Only 1 case   | 0                | 0                | 0             |
| R <sub>1</sub>    | 3                | 18               | 8.4           | 3                | 15               | 7.4           |
| R <sub>2</sub>    | 9                | 22               | 15.7          | 10               | 25               | 16.0          |
| R <sub>3</sub>    | 1                | 24               | 10.0          | 1                | 24               | 12.6          |
| R-CF <sub>1</sub> | 0                | 6                | 3.0           | 0                | 7                | 3.0           |
| R-CF <sub>2</sub> | 0                | 14               | 5.3           | 0                | 11               | 5.5           |
| R-CF <sub>4</sub> | 4                | 20               | 13.2          | 2                | 22               | 9.8           |
| S <sub>1</sub>    | 0                | 10               | 3.1           | 0                | 10               | 3.6           |
| S <sub>2</sub>    | 0                | 6                | 1.9           | 0                | 6                | 1.9           |
| S <sub>3</sub>    | 0                | 10               | 1.1           | 0                | 11               | 0.9           |
| S-CF <sub>1</sub> | 0                | 12               | 7.0           | 0                | 14               | 7.4           |
| S-CF <sub>2</sub> | 0                | 22               | 11.5          | 0                | 18               | 11.6          |
| S-CF <sub>4</sub> | 0                | 20               | 8.7           | 3                | 20               | 10.0          |
| T <sub>1</sub>    | 1                | 6                | 2.7           | 1                | 4.5              | 2.2           |
| T <sub>2</sub>    | -1               | 4.5              | 2.4           | 1                | 4                | 2.0           |
| T <sub>3</sub>    | -2               | 2.5              | -0.27         | -2.5             | 1                | -0.54         |
| T-CF <sub>1</sub> | 0                | 2                | 1.22          | 0                | 3                | 1.43          |
| T-CF <sub>2</sub> | 1                | 8                | 3.29          | 1.5              | 7                | 3.36          |
| T-CF <sub>4</sub> | 1                | 6                | 3.21          | 2                | 7                | 3.47          |
| Axis              | 0°               | 125°             | +66.9°        | -12°             | +128°            | +7.4°         |

case the rate was faster after the bout (average 115 beats per minute) than before. Sinus arrhythmia was common before the matches, but was absent or slight at the higher rates after the matches.

*P-R Interval.*—The P-R interval varied from 0.12 to 0.17 second, but in individual cases there was almost no change after exercise. The average value was 0.149 second.

*QRS Time.*—The values varied from 0.06 to 0.09 second, with no change in individual cases before and after the matches. The average value for the seventy tracings was 0.074 second.

*Q-T Interval.*—In many cases there was no change in the Q-T interval, but with marked increases in rate following exercise the Q-T interval tended to decrease. The average value before the matches was 0.306 second, and after, 0.326 second. No corrections were made for changes in rate.

*P Waves.*—There was a marked change in the height of the P waves in Leads II and III, in which, in almost every case, there was a peaking after exercise; the average values increased 0.7 mm. in Lead II and 0.66 mm. in Lead III after exercise. These figures were treated sta-

tistically, and the changes were found to be significant. No notching of consequence was present in any of the records.

*Q Waves.*—In only six of the seventy records were  $Q_1$  waves present, and these were only 1 mm. in five cases and 1.5 mm. in the sixth case.

Seventeen (24.3 per cent) of the tracings had  $Q_2$  waves; the largest was 4 mm., and, in this case,  $Q_3$  was 7 mm. (see below).

$Q_3$  was more common; it was present in thirty-four (48.6 per cent) of the seventy electrocardiograms. The largest value was 7 mm., and, in this case, it was slightly over one-fourth of the major deflection in any lead. All other  $Q_3$  deflections were less than one-fourth of the major deflection. Exercise had practically no effect on the size of the Q waves.

Only three (4.3 per cent) of the tracings showed Q waves in any of the precordial leads, and only one of these (1 mm.) was in Lead  $CF_4$ .

*R Waves.*—The average values of the R deflections may be seen in Table I. There was a slight tendency for  $R_1$  to decrease in amplitude following exercise, and for  $R_3$  to increase. R in  $CF_4$  also decreased after exercise.

*S Waves.*—The S deflections showed a tendency opposite to that of R; they increased slightly in Leads I and  $CF_4$  after exercise, and decreased in Lead III.

*T Waves.*—There were no negative T waves in Lead I, and only one in Lead II, after exercise, whereas  $T_3$  was negative in forty (55.5 per cent) and diphasic in eight (11.4 per cent) of the seventy tracings. A reversal of sign of the  $T_3$  wave after exercise occurred in four cases; it changed from positive to negative in three cases, and from negative to positive in one case. Three instances of a diphasic T were found in the precordial leads, but none of these were in Lead  $CF_4$ . In general, the T waves in the standard leads decreased in amplitude after exercise, whereas in the precordial leads they increased slightly in amplitude.

*U Wave.*—Nineteen of the electrocardiograms showed definite U waves, and all occurred before exercise when the rate was low. U waves were probably present in other cases, but, because of low amplitude and interference, they were not discernible.

*Axis Deviation.*—One subject had an axis of less than  $0^\circ$  (left), and in five cases it was more than  $90^\circ$  (right). The average axis before exercise was  $66.9^\circ$ , and, after exercise,  $74.4^\circ$ . Twenty-four subjects showed an increasing left axis (average  $13^\circ$ ) after exercise, and nine showed a decreasing left axis (average  $-8.1^\circ$ ) following exercise. Four of these nine subjects were in the right axis range (over  $90^\circ$ ) before exercise.

*QRS Complex.*—Minor degrees of slurring and splitting of this group were common in all leads, but were most pronounced in Leads III,  $CF_1$ , and  $CF_2$ . There were no definite changes following exercise.

*S-T Segment.*—In the three standard leads the S-T segment was isoelectric in all cases, but slight elevations, never exceeding 1 mm., were common in the precordial leads, particularly in Lead CF<sub>2</sub>, in which lead twenty-two of the tracings showed elevations of 1 mm.

*Extrasystoles.*—Ventricular extrasystoles were present in only one case, and occurred in this boy following his bout. No auricular extrasystoles were found.

#### DISCUSSION

From this study we have no evidence that trauma of this nature to the chest wall causes any changes in the heart except in Case A21, in which there was inversion of T<sub>2</sub> and T<sub>3</sub> following exercise, and in Case B14, in which ventricular extrasystoles appeared after exercise. These are nonspecific changes, however, and might be due to any one of a number of causes. Different results might be expected if a similar study were made on a group of older men, for age changes and arteriosclerosis might be present and act as a predisposing factor to injury from indirect trauma. It is usually in these later age groups that such injury occurs.

The average values of the various deflections in the electrocardiograms correspond fairly well with those given in the literature for similar groups. Naturally, there are minor differences due to the position of the subject, emotional stress, and such factors. It has been of great interest to us to note the diversity of the tracings in a group of normals. We feel that it would be wise for anyone who is doing routine electrocardiographic interpretation to study such a group carefully in order to refrain from reading too much into routine tracings.

The changes after exercise were of considerable interest. There was an almost universal increase in the height of P<sub>2</sub> and P<sub>3</sub>, with a tendency to sharpening and pointing of the waves. Whether this was due simply to an increase in rate or to actual increase in intra-auricular pressure cannot be ascertained.

There was also a definite decrease in the height of the T waves in the standard leads following exercise, with an increase in the T waves of the precordial leads. This is in disagreement with the work of Barker, Schrader, and Ronzoni,<sup>6</sup> who studied four normal subjects before and after exercise and concluded that "exercise is followed by acidosis and by a striking increase in the amplitude of the T waves."

Pudda<sup>7</sup> reported only slight changes in the standard leads after exercise, and Jaffe<sup>8</sup> noted an increase in "the angle alpha" for P and T waves after exercises.

Our results are in agreement with those of Barker, Schrader, and Ronzoni as far as T<sub>3</sub> is concerned, for it became increasingly negative after exercise. Some of these discrepancies may be explained by differ-

ences in the interval which elapsed between cessation of the exercise and taking of the tracings.

#### SUMMARY

1. Electrocardiograms of thirty-five young boxers were taken before and after matches.

2. Following exercise there were a definite increase in the height of  $P_2$  and  $P_3$  and a decrease in the size of the T waves.

3. There is no evidence from this study that boxing has any traumatic effect on the normal heart in this age group.

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## THE RECORDING OF THE FETAL ELECTROCARDIOGRAM

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THE possibility of making a reliable graphic record of the fetal heart beat has interested both the cardiologist and the gynecologist for a long time. Such a record would be of great value to the gynecologist for practical clinical use, and to the clinical investigator as a new method of approach to certain problems in fetal physiology.

In the past the electrocardiograph has been used extensively in this study. In addition to the three customary leads, abdominal, vaginal, and rectal leads have been tried, but none of these have met with much success. Hoff, et al.,<sup>1</sup> in a recent paper, reviewed the earlier literature on this subject. They pointed out that the main difficulty has been the low electromotive force of the fetal heart, resulting in small fetal waves which are easily obscured when superimposed on the small irregularities in the electrocardiographic record.

Most of the published curves showing the fetal waves which were obtained with the customary electrocardiograph are, on the whole, not convincing, although during the last several weeks of pregnancy a good degree of success was obtained.<sup>2</sup> Occasionally the fetal electrocardiogram is recorded by accident.<sup>3</sup>

A new and much more successful approach, of which we were unaware at the time we began our work, was made by Bell,<sup>4</sup> who used a modified balanced-input, amplifier system of Matthews. He obtained records with abdominal leads from thirty-three pregnant women within two months of term, of which ten were "positive," eleven were "doubtful" and twelve were "negative." Two additional records, taken at four and 4.5 months of pregnancy, did not show fetal waves. The earliest positive record was taken thirty-four days before delivery. In one of two cases of twin fetuses a double set of fetal waves was recorded.

Having available a more sensitive apparatus, we undertook a study of the fetal electrocardiogram throughout pregnancy.

### METHOD

Recordings were made with a 3-channel, balanced amplifier and crystograph,\* an instrument developed to record electroencephalograms. Time constants of "0.2" for low frequencies and "3" for high frequencies were effective if potential

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\*Offner amplifiers, numbers 140 and 340; and Offner crystograph, 500A.

changes associated with respiration, etc., were not too prominent. In the latter instance a time constant of "0.02" and, at times, "0.002," was used for damping low frequencies (mechanical damping of the vibrations of the writing pen by pressure was necessary in order to make this effective). Leads were taken from the abdomen with the nonpolarizing suction electrodes described by Andrews,<sup>5</sup> or by means of flat metal discs in electrode jelly, held in place by adhesive tape. We found the latter type somewhat more satisfactory. The ground electrode was placed on the lower part of the left thigh. Three abdominal leads were usually used, and were placed to form an equilateral triangle over the uterus. The size of the triangle depended on the height of the fundus because the midline electrode was placed at approximately the level of the top of the fundus. The other two were placed over the right and left lower quadrants of the abdomen. Tracings were taken from all combinations of these four leads, and three different leads were recorded simultaneously. The curves were recorded by the crytograph on paper, with ink, making a permanent record. No developing is necessary, as with the usual type of electrocardiogram.

Deflections caused by the maternal heart beat were always recorded from pairs of the three abdominal leads, and usually from these in combination with the ground lead. Deflections produced by the fetal heart beat were clearly recognizable in a large percentage of the cases. Increasing the amplification of the potentials in questionable cases was effective in spite of the accompanying amplification of artifacts. This was true especially when the time constant for the low frequencies was reduced, and the writing arms were mechanically damped.

We calculated the length of pregnancy by assuming that conception occurred fourteen days after the beginning of the last normal menstrual flow.

## RESULTS

Several kinds of waves are ordinarily recorded in tracings obtained from the abdomen. Most prominent are the deflections caused by the maternal heart beat. These vary in size, but usually have an average deflection of about 200 microvolts.\* The fetal deflections are usually much smaller, and measure about 30 microvolts. In addition, there are often many irregular, small waves of varying size. The exact origin of these is not clear at present. The fetal waves usually appear in one lead, and frequently in several leads.

We have taken forty-six records at various stages of pregnancy (Fig. 1). In thirty-one of these, deflections produced by the fetal heart beat were clearly present, and these records were graded as positive (67 per cent). The remainder showed no definite fetal deflections, and were therefore negative, except one which was questionable.

It will be seen from Fig. 1 that no positive tracing was obtained earlier than the sixteenth week of pregnancy, and that there is a sharp dividing line between the positive and negative records near the end of the fourth month. From the sixteenth week onward there were thirty-eight records. Thirty-one of these were positive (82 per cent). Photographs of sample records, showing positive curves during

\*Deflections of the ordinary string galvanometer electrocardiogram are about 2 to 3 millivolts for an adult heart. One millivolt equals 1,000 microvolts.



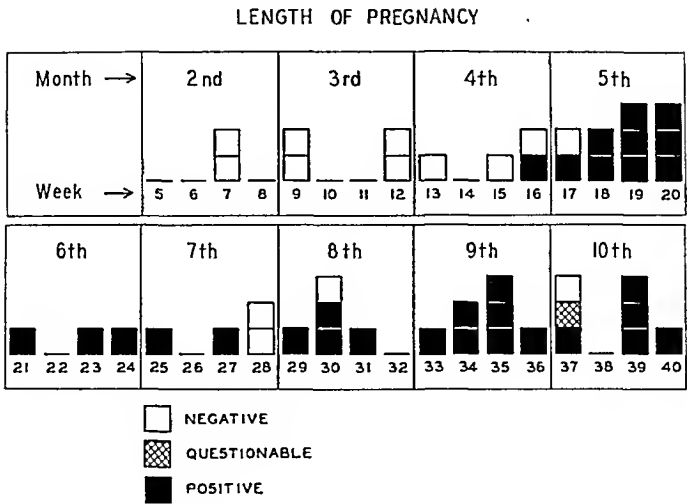


Fig. 1.

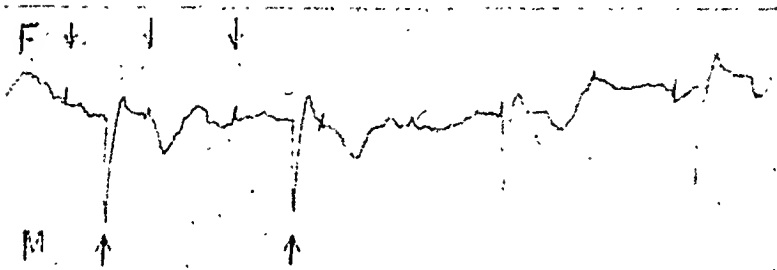


Fig. 2.—Seventeenth week of pregnancy. Heart rates: fetal, 152; maternal, 69.

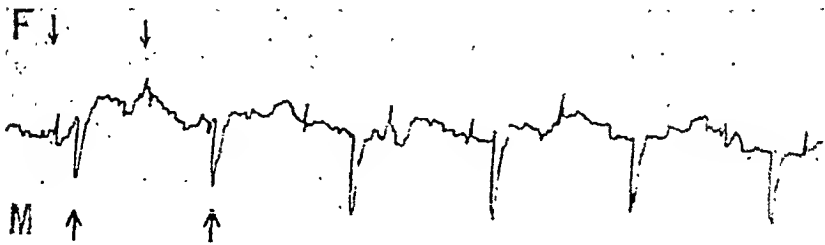


Fig. 3.—Eighteenth week of pregnancy. Heart rates: fetal, 150; maternal, 91.

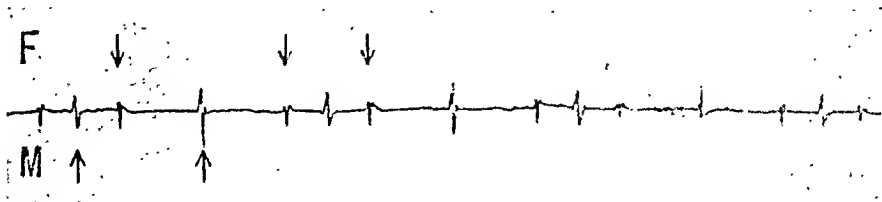


Fig. 4.—Twentieth week of pregnancy. Heart rates: fetal, 152; maternal, 103. Note relative large size of fetal complexes compared with maternal. In this portion of tracing every alternate maternal complex is almost synchronous with a fetal complex. An ordinary electrocardiograph using abdominal leads failed to record deflections of the fetal heart.

the seventeenth, eighteenth, twentieth, twenty-fifth, thirtieth, thirty-fourth, and thirty-eighth weeks of pregnancy, appear in Figs. 2-8.

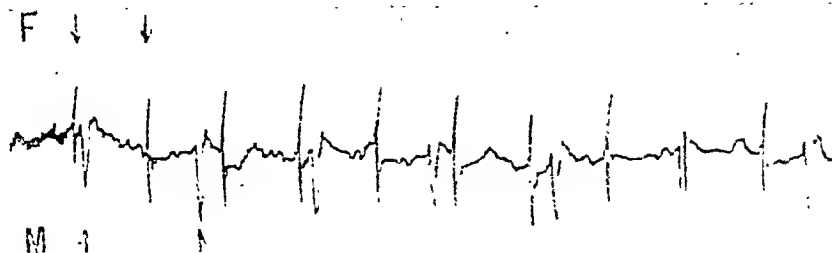


Fig. 5.—Twenty-fifth week of pregnancy. Heart rates: fetal, 158; maternal, 100. Note large fetal complexes.

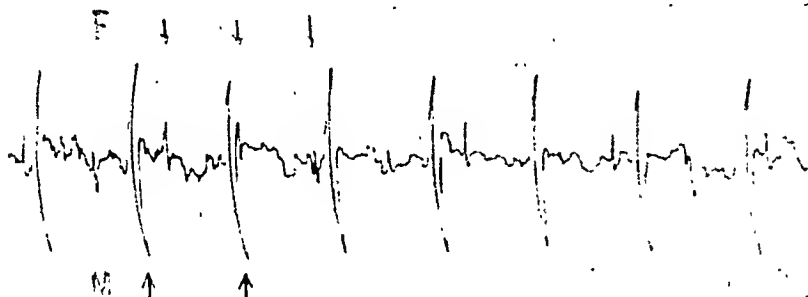


Fig. 6.—Thirtieth week of pregnancy. Heart rates: fetal, 162; maternal, 133.



Fig. 7.—Thirty-fourth week of pregnancy. Heart rates: fetal, 155; maternal, 74.

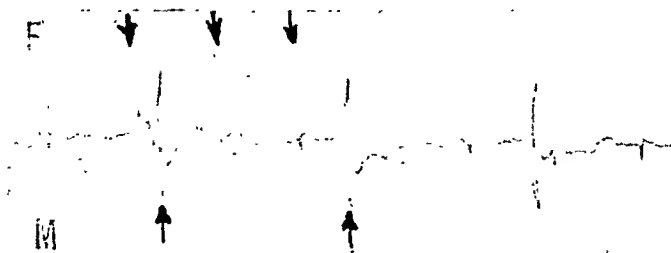


Fig. 8.—Thirty-eighth week of pregnancy. Heart rates: fetal, 148; maternal, 72.

For the purpose of comparison, records were obtained with the ordinary electrocardiographic apparatus and with Offner amplifier and crystograph from one patient, on the same day, using the same leads,

The former instrument, even with double standardization, failed to show any fetal waves; however, good fetal waves were obtained with the crystograph (Fig. 4).

#### DISCUSSION

Soon after the beginning of this study it became obvious that it was possible to record the fetal electrocardiogram earlier than the last two months of pregnancy, the earliest time recorded in the literature.<sup>4</sup> It then became of great interest to ascertain how early in fetal life it could be recorded. Although our earliest record was obtained in the sixteenth week, we suspect that positive records can be obtained earlier. The absolute minimum will be determined by the stage at which the fetal heart develops enough electromotive force to allow recording from leads on the maternal abdominal wall or in a body orifice. The embryology of the heart has some bearing on this aspect of the problem.

According to Arey,<sup>6</sup> the heart tubes fuse in the human embryo and the heart begins to beat at about 3.5 to four weeks. At this stage the embryo has sixteen to thirty-eight somites. In the rat, however, Goss<sup>7</sup> has observed that a small group of cells in the tubular anlage of the heart begins to contract at the three-somite stage. This is prior to the fusion of the tubes. Hoff, et al.,<sup>1</sup> found recognizable P-QRS-T waves at the twenty-somite stage (forty-two hours) in chickens. By the twenty-four-somite stage (forty-eight hours) the complexes were well developed, and in the 4-day-old embryo the electrocardiogram was very much like the adult chicken pattern.

It has been established by studies of human fetuses removed by operation that electrical impulses arising from the heart can be obtained with the electrocardiogram during the first four months of fetal life. Heard, Burkley, and Schaefer<sup>8</sup> studied eleven such fetuses. They recorded electrocardiograms, with chest leads, from fetuses of 9.5, 11.5, 12.5, 13, and 14 weeks of age. Marcel and Exchaquet<sup>9</sup> made a similar study of five cases. They were able to record waves similar to those of an adult at an early age. There is a discrepancy between the fetal ages and their sizes, in these five cases, and, according to accepted data of Arey,<sup>6</sup> they must have been somewhat older than the ages recorded. The earliest electrocardiogram with a pattern similar to that of the adult was obtained from a fetus which was probably about 6 to 7 weeks of age. Eashby<sup>10</sup> recorded the electrocardiogram of another fetus which was 4.5 months old.

In the early stages of fetal life it is doubtful whether the electrical potentials of the fetal heart, as obtained with leads on the maternal abdominal wall, are great enough to be distinguished, because of the small irregular waves that are recorded from extraneous sources. That the potentials are present is indicated by the fact that they can be

recorded directly from the fetus itself. However, in view of the data in the preceding paragraph, it is theoretically possible to obtain fetal electrocardiograms with maternal abdominal leads after the fifth or sixth week of fetal life.

The problem of recording the fetal electrocardiogram earlier than the sixteenth week will probably resolve itself into one of technical improvement of the method. Since the beginning of the study our technique has undergone several improvements. At present our percentage of positive records during and after the seventeenth week of pregnancy is much higher than it was early in the study. It may be that with further improvement it will be even higher. However, the overall percentage of a method such as this is not important except as a general indicator of its usefulness. A positive record indicates that the intra-abdominal fetal heart is beating, and is of a great deal more importance than a negative record. As Bell<sup>4</sup> has said, "It can at least be said in its favour that, unlike many biological tests for pregnancy, it would not be expected to produce any false positives."

Abnormalities of the fetal heart rate have recently been emphasized as a good indicator of distress caused by anoxemia.<sup>11</sup> By means of this method, the fetal heart rate may readily be counted.

It seems to us that the present method has several advantages. After the initial expense of the instrument, an electrocardiogram can be taken at a very small cost. It is rapid, requiring only five to ten minutes. If the curve contains fetal waves, it proves that the fetal heart is beating. It is vastly superior to the ordinary electrocardiograph for recording fetal waves because of its greater sensitivity.

The method is useful clinically in the diagnosis of pregnancy, in ascertaining whether the fetus is living, in the diagnosis of multiple pregnancy (two or more sets of fetal waves), and, experimentally, as a tool for studying certain problems in fetal physiology.

The method has certain disadvantages. The machine is not commonly used at present except in research laboratories, although it may be no more difficult to operate than an ordinary electrocardiograph. The many small, irregular waves which appear on some tracings occasionally obscure the fetal waves. These can usually be eliminated by changing the time constants, thus bringing out the fetal waves and smoothing out the base line.

#### SUMMARY

An improved method for recording the fetal electrocardiogram is described; it uses the 3-channel electroencephalograph and cystograph ink writers.

Fetal waves were recorded successfully from the seventeenth week of pregnancy onward, and 82 per cent of the tracings taken during this period were positive.

Certain advantages and uses of the method are indicated.

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## A STUDY OF SEVENTY RHEUMATIC FAMILIES

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RHEUMATIC fever today remains a major pediatric problem. The results of efforts to discover the etiological agent have been, for the most part, disappointing. The familial nature of rheumatism has long been recognized, and familial epidemiology offers an approach to the study of the disease.

Reports of the incidence of rheumatism in other members of families with rheumatic children have varied considerably, but all agree that there is an increased incidence of rheumatism in such families. What specific factor is responsible for the high familial incidence, however, is a controversial matter. Paul and Salinger<sup>1</sup> have noted that an epidemic of upper respiratory infection in families with a rheumatic member is often followed by the appearance of active rheumatism in several members of the family. They have noted also that such waves of rheumatism often occurred without any precipitating cause. Similar epidemics have been reported in schools, camps, hospital wards, and convalescent homes. Coburn<sup>2</sup> concluded that the "rheumatic state," as he called it, is a special type of response to chemical substances produced by infections of the upper respiratory tract. His observations pointed toward the hemolytic streptococcus as an etiological agent. The high family incidence is explained by this theory, with respect to both an hereditary predisposition and communicability. Numerous investigations have implicated other organisms as specific etiological agents. Recently, evidence that the cause is a filtrable virus has appeared in the literature.

Wilson,<sup>3</sup> in a recent study from New York, concluded that hereditary susceptibility underlies the familial incidence of the disease, although the possibility of other factors is conceded. She found no evidence of a contagious factor or any etiological relationship between respiratory infections and rheumatic fever. Read, Cioeco, and Taussig,<sup>4</sup> in a study from Baltimore, likewise concluded that heredity is the prime factor in the familial incidence. In addition, they had evidence which indicated that association with active rheumatism was also a factor.

A dietary deficiency as a possible factor underlying the high familial trend suggests itself. Rinchart, et al.,<sup>5</sup> have presented experimental and clinical evidence to indicate that vitamin C deficiency is an important factor. This work, however, has been challenged by Sendroy and

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Schultz.<sup>6</sup> A dietary study by Sadow, Hubbard, and Jones<sup>7</sup> did not show that diet was particularly related to rheumatic infection.

All who have studied the epidemiology of rheumatism agree that it is a disease of the lower economic classes. Findlay<sup>8</sup> found that not the very poor, but the between-class poor families, were those who suffered chiefly. The majority of the families in the group studied by Wilson<sup>3</sup> were those of the moderately well-to-do laboring class, with incomes of from \$1,500 to \$2,600 per year. Rheumatism is not rare, however, in the well-to-do classes. Findlay<sup>8</sup> reported fifteen well-to-do families which he had observed in fifteen years. Of these, 60 per cent had more than one rheumatic member. Coburn<sup>2</sup> studied a group of healthy student nurses at the Presbyterian Hospital in New York. They lived in excellent surroundings, without overcrowding, and had an adequate diet. In one year (1928) he found that 10 per cent of the group became ill with rheumatic disease. Upper respiratory infection was the only factor that could be associated with these cases.

The material for this study consists of seventy families, each of which has a rheumatic child attending the Christopher Public School. The family studies were begun in December, 1938, although many of the children were under observation in school for a longer time. We visited each home, and all available members of the family were examined, that is, the siblings, parents, grandparents, aunts, uncles, and cousins. Careful histories were taken of all members of the family, including those who were not available and those who had died. Whenever possible, the histories were checked with the clinic and hospital records. Social conditions were noted in relation to the rheumatic infection as they existed at the various periods. The diet habits were investigated, and food diaries were kept by each family. Follow-up visits were made when necessary. The dietary and social data were compiled and analyzed by one of us (R. L. R.), who is an experienced welfare nutritionist. Frequent follow-up visits were made by the school nurse, so that new developments were constantly recorded. It was felt that, by direct contact between us and the families in their homes, a more reliable survey could be made than if the data were obtained by other means which are frequently used.

The largest problem encountered in this study was the accurate diagnosis of rheumatism. It is very likely that the variations in the figures quoted on the incidence of rheumatism are partly due to different criteria for diagnosis. It is unfortunate that there is no specific test for rheumatism such as there is for tuberculosis. In this study, only those cases which were believed to be unquestionably rheumatic were included. The signs and symptoms considered to be diagnostic of rheumatism were (1) migratory polyarthritis, associated with other signs of general infection, and not caused by other specific disease, (2) chorea, (3) characteristic signs of rheumatic heart disease, (4) rheumatic nodules, and (5) rheumatic erythema.

It is important to differentiate the arthritis of rheumatic fever from other forms of arthritis, especially chronic infections, or rheumatoid, arthritis. The latter usually causes deformities, but these are never found in rheumatic fever. Nodules are also sometimes seen in rheumatoid arthritis, and may be almost indistinguishable from true rheumatic nodules. However, the other manifestations will easily clarify the diagnosis. In this series, every patient with nodules also had definite rheumatic heart disease.

There are other signs and symptoms that are commonly found in rheumatic fever, but are not diagnostic of the disease. These are epistaxis, pallor, nervousness, loss of weight, abdominal pain, low-grade fever, anorexia, fatigue, anemia, and "growing pains." In the absence of more definite signs, however, none of these symptoms is diagnostic of rheumatic infection, and they are often encountered in other conditions. Children with these symptoms have sometimes been called prerheumatic subjects. However, whether there is a prerheumatic state is a much discussed subject. Findlay<sup>8</sup> found that in the great majority of his cases the onset was sudden and the symptoms clearly defined.

The significance of "growing pains" is debatable. Symptoms which are called "growing pains" frequently may be traced to a variety of causes, including foot strain, aching muscles, and epiphysitis. Many children have so-called "growing pains" with no demonstrable cause, and, on subsequent examination, do not generally show evidence of rheumatic heart disease. Although some "growing pains" are undoubtedly rheumatic, other manifestations must be present to confirm this diagnosis.

The interpretation of murmurs is another difficult problem. In the presence of the typical signs of mitral regurgitation or stenosis, there is little doubt of the rheumatic nature of the disease. However, systolic murmurs are often heard in normal children, and it is important not to confuse such harmless murmurs with those indicative of mitral disease. A soft systolic murmur which was maximum over the second left intercostal space was commonly encountered, but was not considered significant. A soft systolic murmur which was heard best over the lower part of the precordium, inside the apex, with slight transmission, was also considered functional unless it was accompanied by other signs of organic heart disease. Apical systolic murmurs are more significant. They are seen constantly in febrile conditions, and often in anemia, unassociated with rheumatism. However, a blowing systolic murmur which is maximum at the apex and is transmitted to the left, often replacing the first tone, is usually diagnostic of mitral insufficiency, especially if there is an accentuated pulmonic second sound. The other signs of rheumatic disease need not be discussed at this time. Most of our patients have been followed in clinics, and the diagnoses have been confirmed by roentgenograms and electrocardiograms. It is felt that by



TABLE I

|  | ROSENBLUM |      | WILSON |      | READ |      | FINDLAY |      | FAULKNER<br>AND<br>WHITE |      | IRVINE-<br>JONES |    | STROUD |    | ST.<br>LAWRENCE |      |
|--|-----------|------|--------|------|------|------|---------|------|--------------------------|------|------------------|----|--------|----|-----------------|------|
|  | NO.       | %    | NO.    | %    | NO.  | %    | NO.     | %    | NO.                      | %    | NO.              | %  | NO.    | %  | NO.             | %    |
| <i>A. Family Incidence—Parents and Siblings</i>                    |           |      |        |      |      |      |         |      |                          |      |                  |    |        |    |                 |      |
| Total families   | 70        |      | 112    |      | 33   |      | 701     |      | 200                      |      | 167              |    | 141    |    | 100             |      |
| Families with multiple rheumatic siblings                          | 13        | 18.6 |        |      |      | 27.3 | 39      | 5.5  |                          |      | 499              |    |        |    |                 |      |
| Families with rheumatic parents                                    | 19        | 27.2 | 55     | 44.5 |      | 51.5 | 131     | 18.6 |                          |      |                  |    |        |    |                 |      |
| Families with multiple rheumatic siblings and/or rheumatic parents | 27        | 38.6 |        |      | 20   | 60.6 |         |      | 71                       | 35.5 | 54               | 32 |        | 31 | 50              | 50   |
| <i>B. Parents and Siblings Listed as Individuals</i>               |           |      |        |      |      |      |         |      |                          |      |                  |    |        |    |                 |      |
| Siblings of index cases  | 322       |      | 387    |      | 110  |      |         |      |                          |      |                  |    |        |    |                 |      |
| Rheumatic siblings of index cases                                  | 20        | 6.2  | 133    | 34.4 | 17   | 15.5 |         |      |                          |      |                  |    |        |    |                 |      |
| Parents—rheumatic  | 20        | 14.3 |        |      | 20   | 30.8 |         |      |                          |      |                  |    |        |    |                 |      |
| Total parents and siblings of index cases                          | 462       |      |        |      | 175  |      |         |      | 1235                     |      |                  |    |        |    | 480             |      |
| Total rheumatic persons in above group                             | 40        | 8.65 |        |      |      | 21.0 |         |      |                          | 8.79 |                  |    |        |    | 71              | 14.8 |
| <i>C. Other Family Members</i>                                     |           |      |        |      |      |      |         |      |                          |      |                  |    |        |    |                 |      |
| Total families   | 70        |      |        |      | 96   |      | 701     |      |                          |      |                  |    |        |    |                 |      |
| Families with additional rheumatic members                         | 35        | 50   |        |      |      |      | 243     | 34.7 |                          |      |                  |    |        |    |                 |      |
| Families with rheumatic grand-parents                              | 4         | 6.5  |        |      |      | 57.0 | 32      | 4.5  |                          |      |                  |    |        |    |                 |      |
| Families with rheumatic aunts, uncles, cousins                     | 12        | 17.1 |        |      |      |      | 72      | 10.2 |                          |      |                  |    |        |    |                 |      |
| No. of rheumatic grandparents                                      | 4         | 1.4  |        |      |      |      |         |      |                          |      |                  |    |        |    |                 |      |

Findlay, Glasgow, 1931.  
Faulkner and White, Boston, 1934.  
St. Lawrence, New York, 1922.  
Stroud, Philadelphia, 1933.  
Irvine-Jones, St. Louis, and Toronto, 1933 (two series).  
Read, Baltimore, 1938-1939.  
Wilson, New York, 1940.

using the above criteria there can be little doubt about the rheumatic nature of the cases so designated.

The family incidence of rheumatism, together with a comparison of studies in other localities, is shown in Table I. We found that approximately two-fifths of the families had at least one additional rheumatic member among parents or siblings, as did Faulkner and White,<sup>9</sup> of Boston. This makes an incidence of 9 per cent in terms of individuals. Fourteen per cent of the parents and 6 per cent of the siblings were involved. Stroud, et al.,<sup>10</sup> of Philadelphia, and Irvine-Jones,<sup>11</sup> with studies from St. Louis and Toronto, reported similar results. Coburn,<sup>2</sup> of New York, found about one-third of a group of 162 families involved. Although our figures are considerably higher than those of Findlay,<sup>8</sup> of Glasgow, they are much lower than those of Wilson,<sup>3</sup> of New York, and Read, et al.,<sup>4</sup> of Philadelphia. A large incidence was also found in relatives other than parents and siblings. At least one other member was found to be rheumatic in one-half of the seventy families studied.

TABLE II

FAMILY INCIDENCE AS INFLUENCED BY DIFFERENT CRITERIA FOR DIAGNOSIS

|  | DEFINITE<br>RHEUMATIC<br>CASES |      | INCLUDING<br>QUESTIONABLE<br>CASES |      |
|--|--------------------------------|------|------------------------------------|------|
|  | NO.                            | %    | NO.                                | %    |
| Families with other rheumatic members  | 35                             | 50   | 45                                 | 64   |
| Families with other rheumatic siblings | 13                             | 18.6 | 29                                 | 41.4 |
| No. of other rheumatic siblings        | 20                             | 6.2  | 51                                 | 15.9 |
| Families with rheumatic parents        | 19                             | 27.2 | 30                                 | 42.8 |
| No. of rheumatic parents               | 20                             | 14.3 | 33                                 | 23.6 |
| Families with rheumatic grandparents   | 4                              | 6.5  | 6                                  | 8.6  |
| No. of rheumatic grandparents          | 4                              | 1.4  | 6                                  | 2.25 |

The variations in the incidence may be attributed, to some extent, to geographic factors and to yearly variations in the occurrence of rheumatism. They may be due also to chance differences in the sampling. It has already been pointed out that differences in the criteria for diagnosis could be responsible for some discrepancies. The great extent to which this could influence the results is shown in Table II. We have included in the first group only those cases which we feel were unquestionably rheumatic. In the second group are included patients with symptoms and signs which could be mistaken for rheumatic heart disease or rheumatism. These include cases of chronic arthritis, traumatic arthritis, and functional and congenital murmurs. The unreliability of histories was brought out clearly. Children who were thought to have organic heart disease were frequently found to have functional murmurs, with no evidence of previous rheumatic attacks. On the other hand, many cases of unsuspected rheumatic heart disease were discovered in both parents and children.

The number of rheumatic siblings per family is shown in Table III; this varied from one to six, and in one family six of eight children had demonstrable rheumatic heart disease. This latter family also had a rheumatic mother. Table IV shows the total number of rheumatic persons per family, including the parents. This varied from one to seven.

TABLE III  
NUMBER OF RHEUMATIC SIBLINGS PER FAMILY

|                                      |     |    |   |   |   |   |
|--------------------------------------|-----|----|---|---|---|---|
| No. of families                      | 57  | 10 | 1 | 1 | 0 | 1 |
| Total no. of siblings                | 293 | 74 | 8 | 9 | 0 | 8 |
| No. of rheumatic siblings per family | 1   | 2  | 3 | 4 | 5 | 6 |

TABLE IV  
NUMBER OF RHEUMATIC PERSONS PER FAMILY (PARENTS AND SIBLINGS)

|                                     |    |    |   |   |   |   |   |
|-------------------------------------|----|----|---|---|---|---|---|
| No. of families                     | 43 | 20 | 4 | 2 | 0 | 0 | 1 |
| No. of rheumatic persons per family | 1  | 2  | 3 | 4 | 5 | 6 | 7 |

The relation of parental rheumatism to rheumatism in the children is indicated in Table V. In families in which one or both parents were rheumatic, there was a higher incidence of rheumatism in the children. This is reflected in the percentage of families and siblings involved. Index cases\* were not included in this calculation.

TABLE V  
INCIDENCE OF RHEUMATISM IN FAMILIES WITH RHEUMATIC AND NONRHEUMATIC PARENTS

| A. CONSIDERING FAMILIES |  |   |          |
|-------------------------|--|---|----------|
| PARENTAL GROUP          | NO. OF FAMILIES                          | NO. OF FAMILIES WITH OTHER RHEUMATIC SIBLINGS | PER CENT |
| Both parents negative   | 51                                       | 8   | 15.7     |
| One or both positive    | 19                                       | 5   | 25.6     |
| B. CONSIDERING SIBLINGS |  |   |          |
| PARENTAL GROUP          | TOTAL NO. OF SIBLINGS EXCEPT INDEX CASES | RHEUMATIC SIBLINGS                            | PER CENT |
| Both parents negative   | 250                                      | 10  | 4        |
| One or both positive    | 72                                       | 10  | 13.9     |

A comparison of the incidence prior to and after association with patients in the active stage of the disease is demonstrated in Table VI. This is shown both for the group as a whole, and for families with positive and negative parental histories. The method used was the same as that employed by Read, Cioceo, and Taussig<sup>4</sup> in a similar study in

\*By "index cases" we mean the seventy rheumatic children registered in the Christopher School.

Baltimore. The incidence of the disease, in terms of person years, was computed prior to and after association with a patient in the active stage of rheumatism. The first two years of life were not included because of the rare incidence of rheumatism at this age. Index cases were omitted in order not to bias the data. The results indicate that the incidence of rheumatism is about two and one-half times higher after, than prior to, association with a person who has the disease in an active stage. Again, it is evident that families with rheumatic parents show a higher incidence. These observations confirm the results of Read and her co-workers,<sup>4</sup> but our figures are generally lower. These data suggest that prolonged contact with a person who has active rheumatism predisposes to the development of new cases, thus implying a contagious factor. However, common environmental conditions may also be operative.

TABLE VI

INCIDENCE OF RHEUMATISM BEFORE AND AFTER ASSOCIATION WITH ACTIVE RHEUMATISM IN CASES PER 1,000 PERSON YEARS

|                    | WHOLE GROUP | NONRHEUMATIC PARENTS<br>51 FAMILIES | RHEUMATIC PARENTS<br>19 FAMILIES |
|--------------------|-------------|-------------------------------------|----------------------------------|
| Before association | 4.55        | 2.25                                | 8.7                              |
| After association  | 10          | 6.6                                 | 20.4                             |

Simultaneous attacks occurred in six of the thirteen families with multiple rheumatic siblings. In one family with four rheumatic siblings, three of them experienced attacks within one month. Attacks among parents and siblings occurred at the same time in four of the nineteen families with rheumatic parents. These simultaneous attacks did not have their onset on the same day, but were separated by several weeks or months. Unlike Paul and Salinger,<sup>1</sup> however, we did not find epidemics of respiratory infections preceding these attacks.

TABLE VII

PREDISPOSING FACTORS IN INDEX CASES

| ASSOCIATED WITH<br>RESPIRATORY INFECTIONS  | NO. | %    | NOT ASSOCIATED<br>WITH RESPIRATORY<br>INFECTIONS | NO. | %    |
|--|-----|------|--|-----|------|
| Upper respiratory infection or sore throat | 15  | 21.4 | Dampness   | 2   | 2.8  |
| Scarlet fever                              | 7   | 10   | Freezing   | 1   | 1.4  |
| Pneumonia                                  | 3   | 4.3  | Psychic trauma                                   | 2   | 2.8  |
| Measles                                    | 3   | 4.3  | Tonsillectomy and adenoidectomy                  | 2   | 2.8  |
| Pertussis                                  | 1   | 1.4  | Nothing  | 34  | 48.8 |
| Total                                      | 29  | 41.4 | Total  | 41  | 58.6 |

The predisposing factors in the seventy index cases are shown in Table VII. The association with respiratory infections is evident. It is

interesting to note that, in 10 per cent of the group, the onset of rheumatism occurred during convalescence from scarlet fever. In about one-half of the cases the first attacks of rheumatism were not preceded by respiratory infections. The reliability of the histories may again be questioned, because sore throats and other upper respiratory infections often go unnoticed in children.

TABLE VIII

RELATION OF TONSILLECTOMY AND ADENOIDECTOMY TO RHEUMATIC RECURRENCES\*

| AGE AT TIME OF OPERATION (YEARS) | TOTAL NO. OF PATIENTS | PATIENTS HAVING RECURRENCES | PER CENT |
|----------------------------------|-----------------------|-----------------------------|----------|
| 0-5                              | 4                     | 3                           | 75       |
| 6-9                              | 18                    | 11                          | 61       |
| 10 and over                      | 12                    | 5                           | 41.6     |
| Total                            | 34                    | 19                          | 55.9     |

\*Eleven of nineteen patients with recurrences had tonsillar stumps. Twelve patients had their first attack subsequent to operation, and four of these had tonsillar stumps.

The relation of tonsillectomy and adenoideectomy to the recurrence of rheumatism is shown in Table VIII. It appears that the age at the time of operation determines the number of recurrences; the older the child, the fewer the recurrences. Since this is the natural course of the disease, tonsillectomy and adenoideectomy do not seem to prevent recurrences. However, eleven of the nineteen patients with recurrences had tonsillar stumps, so that we are not justified in drawing conclusions from these figures. This is a possible source of error in any study dealing with the effect of tonsillectomy and adenoideectomy on rheumatism.

TABLE IX

RELATION OF TONSILLECTOMY AND ADENOIDECTOMY TO SEVERITY OF HEART DISEASE\*

|  | GROUPS |    |     |    |
|--|--------|----|-----|----|
|  | I      | II | III | IV |
| Tonsils out prior to first attack—clean  | 1      | 3  | 4   | 0  |
| Tonsils out prior to first attack—stumps | 1      | 2  | 1   | 0  |
| Tonsils out after first attack—clean     | 3      | 10 | 5   | 4  |
| Tonsils out after first attack—stumps    | 0      | 3  | 5   | 4  |
| Tonsils in                               | 2      | 6  | 9   | 7  |

\*Heart condition is classified as I to IV, mild to severe. The figures indicate the number of cases in each group.

The relation of tonsillectomy to the severity of the heart damage is shown in Table IX. The degree of heart damage was classified as I to IV, varying from mild to severe. There were more cases of severe heart damage among the patients who had no tonsillectomy, or had tonsillectomy after the onset of the disease. These observations are similar to those of Kaiser,<sup>12</sup> who found that the mortality rate was much higher among the patients who either had no operation, or did not have it until after the first attack. He also found that tonsillectomy did not prevent recurrences.

The relation of family income to the incidence of rheumatism in other siblings is shown in Table X. The families were divided into two groups, namely, those receiving some form of relief and the self-supporting. There were thirty-three families in the self-supporting group, and their average yearly income was \$1,460. The highest income of any single family was \$1,800. The average income of the relief group could not be stated because of the varied ways in which the relief was administered. It is safe to assume that the relief group had a slightly lower average income than the private group. A study by the United States Department of Labor, in 1936, showed that one-half of the families in Chicago had incomes under \$1,412, and that one-third of the families had incomes under \$1,000. This included both private and relief families. Hence, although our series represents a low-income group, it is nevertheless representative of one-half of the families of Chicago. The self-supporting group fared worse in the incidence of rheumatism among the siblings. This may be due to a chance variation, but it agrees with the observations of others that rheumatism is not a disease of the extremely poor, but of the upper poor class. The income was also compared with the number and severity of attacks. The results do not permit definite conclusions, but the relief group seemed slightly favored.

TABLE X  
RELATION OF INCOME TO INCIDENCE OF RHEUMATISM IN SIBLINGS

| GROUPS          | TOTAL<br>FAM-<br>ILIES | FAMILIES WITH<br>OTHER RHEUMATIC<br>SIBLINGS |      | TOTAL<br>SIBLINGS | RHEUMATIC<br>SIBLINGS |      |
|-----------------|------------------------|--|------|-------------------|-----------------------|------|
|                 |                        | NO.  | %    |                   | NO.                   | %    |
| Relief          | 37                     | 5  | 13.5 | 160               | 6                     | 3.75 |
| Self-supporting | 33                     | 8  | 24.2 | 162               | 14                    | 8.64 |

A similar study was made of the possible effect of vermin on the incidence of the disease. The results showed no definite correlation.

In Table XI the condition of the homes, with respect to heat and dampness, is compared with the incidence of rheumatism in other siblings. Although one cannot draw conclusions from small groups such as these, it appears that a higher incidence of rheumatism in the sibling is associated with dampness. A comparison of heat and dampness with the number and severity of attacks was also made, but no correlations were noted.

Table XII shows the relation of diet to the incidence of rheumatism. Fifty of the seventy families kept a weekly dietary. This was analyzed from a qualitative standpoint only, for an accurate estimate of the amount of food consumed was not feasible. For this reason the calorie intake was not computed. It was interesting that the diets in general

TABLE XI

RELATION OF HEAT AND DAMPNES IN HOME TO INCIDENCE OF RHEUMATISM IN SIBLINGS

|                                | TOTAL<br>FAM-<br>ILIES | FAMILIES WITH<br>OTHER RHEUMATIC<br>SIBLINGS |      | TOTAL<br>SIBLINGS | RHEUMATIC<br>SIBLINGS |      |
|--------------------------------|------------------------|--|------|-------------------|-----------------------|------|
|                                |                        | NO.  | %    |                   | NO.                   | %    |
| Insufficient heat and dampness | 7                      | 2  | 28.6 | 38                | 4                     | 10.5 |
| Sufficient heat—no dampness    | 41                     | 8  | 19.5 | 191               | 13                    | 6.8  |
| Insufficient heat              | 19                     | 2  | 10.6 | 82                | 4                     | 4.9  |
| Sufficient heat                | 51                     | 11   | 21.6 | 240               | 16                    | 6.6  |
| Dampness                       | 19                     | 5  | 26.4 | 87                | 7                     | 8.05 |
| No dampness                    | 51                     | 8  | 15.7 | 235               | 13                    | 5.53 |

TABLE XII

RELATION OF DIET TO INCIDENCE OF RHEUMATISM IN SIBLINGS

| DIET GROUP* | NO. OF<br>FAMILIES | FAMILIES WITH OTHER<br>RHEUMATIC SIBLINGS |      | NO. OF<br>SIBLINGS | RHEUMATIC SIBLINGS |     |
|-------------|--------------------|---|------|--------------------|--------------------|-----|
|             |                    | NO.                                       | %    |                    | NO.                | %   |
| I           | 10                 | 2   | 20   | 43                 | 6                  | 14  |
| II          | 15                 | 2   | 13   | 64                 | 2                  | 3.1 |
| III         | 15                 | 2   | 13.3 | 84                 | 2                  | 2.4 |
| IV          | 10                 | 3   | 30   | 60                 | 6                  | 10  |

\*Group I, Adequate. Group II, Deficient in vitamin C only. Group III, Inadequate. Group IV, Very poor.

were of the high-protein type. Since most protein foods are relatively expensive, they are usually purchased at the exclusion of other essential foods, especially fruits, vegetables, etc. The United States Government standards for a minimum adequate diet were used in classifying the diet groups. Four-fifths of the families used more than the minimum amount of milk. The diets varied mostly in the use of fresh fruits and vegetables. The families were divided into four groups, according to their food standards. Group I met all of the minimum requirements for an adequate diet. Group II was deficient in vitamin C, but met most of the other requirements. Group III was decidedly deficient in many essential elements. Group IV was the poorest of all.

According to this small series, there is no apparent correlation between diet and family incidence of rheumatism. In two of the families, one with four and the other with six rheumatic siblings, the diet of the former fell into Group IV, and the latter into Group I.

An analysis of the diets, as compared with the number and severity of rheumatic attacks, also failed to show any direct relationship. We must remember, however, that the diets met minimum, not optimum, standards. Only three of the family diets were on an optimum level. This reveals the need for a study of a similar group of families who have optimum diets.

## SUMMARY

A group of seventy low-income families, each with a rheumatic child attending the Christopher Public School, was studied by us in their homes. The following observations were made:

1. There was a marked incidence of rheumatism in other family members.

2. The families with rheumatic parents had a higher incidence of the disease among the siblings than those with nonrheumatic parents.

3. The incidence was higher after association with a person who had active rheumatism. It was higher in families with rheumatic parents than in families with nonrheumatic parents.

4. Simultaneous attacks of rheumatism were frequently noted among siblings, and among parents and siblings. Waves of respiratory infections prior to those attacks were not noted.

5. Respiratory infections occurred preceding the onset of the first manifestations of rheumatism in slightly less than one-half of the cases. Scarlet fever preceded the onset in 10 per cent of the cases. In the cases which were not preceded by respiratory infections, a variety of factors were present, including exposure to dampness, chilling, tonsillectomy, and psychic trauma. There was no illness in a number of cases preceding the onset of the first rheumatic symptoms.

6. Tonsillectomy did not seem to influence rheumatic recurrences. The older the child at the time of tonsillectomy, the fewer the recurrences. Generally, however, the patients with severe heart damage were those who had not had a tonsillectomy, or had had it performed after the onset of the rheumatism.

7. An analysis of the incidence of rheumatism, as compared with the family income, showed a higher incidence in the self-supporting group than in the relief group. The self-supporting group was on a marginal income level, however. There appeared to be no correlation between the number and severity of attacks.

8. There was no correlation between the incidence of rheumatism and the presence of vermin.

9. In an analysis of home conditions, the only factor that could be correlated with an increased incidence of rheumatism was dampness. There was no correlation, however, between dampness and the number and severity of the attacks.

10. No relation between diet and the occurrence of rheumatism could be found. It must be emphasized that most of the families which were studied did not have an optimum diet.



## CONCLUSIONS

1. Although there was some correlation between the incidence of rheumatism and dampness, there was no apparent relationship to other home conditions or to diet. It is to be emphasized, however, that all of the families were at the lower income level.

2. The outstanding observation was the marked familial trend in rheumatic fever, and the tendency toward simultaneous flare-ups in several members of the family.

3. If these results are correct, and studies in other localities bear this out, it would suggest that in dealing with this condition we should pay particular attention to infection in other members of the family. In this way it may be possible to prevent rheumatic infection in susceptible persons and to institute early treatment, once it has occurred.

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## RESTING BLOOD FLOW AND PERIPHERAL VASCULAR RESPONSES IN HYPERTENSIVE SUBJECTS

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THE altered hemodynamics in the hypertensive state in man is still the subject of much speculation and controversy. Obviously, only four factors can be implicated in the production of the elevated blood pressure, namely, cardiac output, blood volume, blood viscosity, and peripheral resistance. There is general agreement that the cardiac output at rest is not increased in this condition,<sup>1</sup> although a number of reports<sup>2</sup> present conflicting and variable observations in this respect. The pertinent investigations on blood volume<sup>3</sup> and blood viscosity<sup>4</sup> likewise suggest that no significant differences exist between normal and hypertensive subjects, although here again there is some disagreement.<sup>5</sup> When it is assumed, however, that the above three factors are unaltered, or, at least, not affected to a degree sufficient to raise blood pressure significantly, the only remaining factor which could possibly account for the hypertensive state is an increase in peripheral resistance. This is the view of most workers in the field.

The question naturally arises as to whether or not this increased peripheral resistance is a generalized one. Since, according to Poiseuille's law, the pressure varies inversely as the fourth power of the radius of a vessel, it is evident that a slight increase in the tonus of the arterioles, even if limited to a single portion of the vascular bed, would be sufficient to cause a significant elevation in systemic blood pressure. Because of this theoretical possibility, together with evidence which, for the most part, is of an indirect nature, the concept that the vasoconstriction producing hypertension occurs chiefly, if not entirely, in the splanchnic area was advanced<sup>6</sup> and was universally accepted until recently.

Prinzmetal and Wilson,<sup>7</sup> using the venous occlusion plethysmographic method, studied thirty-two hypertensive and eighteen normal subjects and found that the average rate of resting blood flow in the forearm was the same in both groups. As a result of these observations, they concluded that the increased peripheral resistance is not limited to the splanchnic region, but exists in the extremities as well, i.e., that the hypertonus is generalized. Pickering<sup>8</sup> utilized the plethysmographic method for the forearm and Stewart's calorimeter for the reflexly vasodilated hand and arrived at a similar conclusion.

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The hand contains specialized blood vessels, the arteriovenous shunts, and blood flow through this vascular bed has been shown to be affected by a variety of vasoconstricting stimuli, even when the vessels are fully dilated.<sup>9</sup> Hence the objection can be raised on purely theoretical grounds that blood flow data obtained on the hand are not representative of peripheral blood flow generally. In the light of the recent work of Grant and Pearson,<sup>10</sup> the same criticism can be applied to a lesser degree to the above-mentioned results with the plethysmograph, for, although blood flow to the forearm was studied, no precautions were taken to prevent a variation in the quantity of venous return from the hand from influencing the determinations.

Stead and Kunkel<sup>11</sup> found that the peripheral vascular reactions of hypertensive patients to exercise and local heat were similar to those of normal subjects. Accepting the hypothesis proposed by Prinzmetal and Wilson, and by Piekerling, they interpreted their observations to indicate that the increased peripheral resistance in the blood vessels of the extremities of hypertensive persons cannot be reduced to a normal level, even by powerful vasodilating agents.

In order to clarify some of these questions, we studied a relatively large number of normal and hypertensive subjects and submitted the data to statistical analysis. Resting blood flow readings were obtained on the forearm, leg, and hand by means of the venous occlusion plethysmographic method; special precautions were taken, in the case of the forearm and leg, to obstruct all venous return from the hand and foot. In addition, the peripheral vascular responses to local anoxemia and exercise were studied, as well as the state of the venous bed.

#### METHOD

The investigation included 160 subjects, of whom seventy were hypertensive and ninety were normal. In the hypertensive group the average systolic blood pressure was 195 mm. Hg; the highest was 255 mm., and the lowest, 150 mm. The average diastolic level was 112 mm.; the highest was 162 mm., and the lowest, 88 mm. In those instances in which the systolic pressure was below 160, or the diastolic below 95, one or the other was always sufficiently elevated to justify placing the subject in the hypertensive group. No attempt was made to classify the patients according to the generally accepted clinical categories, for a clear-cut differential diagnosis was often difficult or impossible to make. No subjects were used who showed any signs of cardiac failure, were suffering from auricular fibrillation associated with a pulse deficit, or manifested obvious arteriosclerotic changes in the lower extremities.

By means of the venous occlusion plethysmographic method, blood flow measurements, in cubic centimeters per minute per 100 c.c. of limb volume, were generally made upon two extremities simultaneously; the technique employed was identical in all respects with that previously reported.<sup>12</sup> The temperature of the water in the plethysmograph was kept at 32° C. During the measurement of blood flow in the forearm and leg, venous return from the hand and foot was prevented by maintaining a pressure which was much higher than the systolic level (350 mm. Hg, or above) at the wrist and ankle.

The routine of our experiments included a number of procedures. Generally, ten to fifteen control, resting, blood flow measurements were made at the beginning

and also at different times during the experiment, so that a satisfactory average might be secured. Then the effect of local anoxemia on peripheral blood flow was studied by applying an arterial occlusion pressure to the extremity, proximal to its insertion into the plethysmograph, for a period of five to ten minutes. Immediately after release of the pressure, blood flow was recorded every ten seconds for five to seven minutes. From these figures a graph was later constructed, and, by means of a planimeter, the number of cubic centimeters of excess blood flow, over and beyond the previously ascertained average resting level, was calculated.<sup>13</sup> The blood flow repayment was expressed as cubic centimeters of excess blood flow per 100 c.c. of limb volume per minute of arterial occlusion.

Next, the peripheral circulatory response to a standard amount of exercise was studied. This was accomplished by having the subject, with the forearm in a plethysmograph, squeeze an ordinary sphygmomanometer bulb in his hand fifty to sixty times in one minute, which was sufficient to raise the pressure in a 5-gallon bottle to 70 mm. Hg. The muscles utilized were, for the most part, limited to those in the forearm. This exercise could be accomplished without difficulty by all hypertensive patients whose general physical condition was good. An attempt was made to equalize the intangible factor of muscular efficiency by excluding any patients who were unable to perform this task, so that the reactions of the remaining hypertensive subjects could more justifiably be compared with those of the normal group.

Immediately after this exercise, blood flow records were obtained at ten-second intervals for four minutes, and thereafter at one-half minute intervals until the blood flow returned to the previous control level. As in the experiments on local anoxemia, in each instance a graph was constructed from the blood flow figures which were obtained, and, by means of a planimeter, the number of cubic centimeters of excess blood flow over and beyond the average control resting level was ascertained.

Finally, in order to obtain some information as to whether or not there is an increased tonus in the venous bed\* in hypertension, the following procedure was carried out upon the forearm and leg. A base line was obtained by raising the recording pen attached to the Brodie's bellows to a mid-position and recording limb volume changes on a slowly moving drum. Since, as previously reported,<sup>14</sup> spontaneous volume changes are minimal in the forearm and leg, a constant base line was readily obtained. A pressure of 10 mm. Hg was then applied to the extremity proximal to its insertion in the plethysmograph, and the increase in the volume of the extremity was recorded on the drum, according to the technique described by Capps.<sup>15</sup> When the base line reached a plateau, the external pressure was again raised 10 mm. Hg. This procedure was continued in 10 mm. steps until a pressure of 70 mm. Hg was reached. The change of volume in the extremity, as recorded with each 10 mm. increment of pressure, was expressed as cubic centimeters of increase per 100 c.c. of limb volume.

In addition to the plethysmographic studies, blood pressure readings and pulse rates were taken at stated times during each experiment. In those instances in which there was some doubt about the presence or absence of congestive heart failure, circulation time measurements, using sodium dehydrocholate,† were also made.

## RESULTS

*Resting Blood Flow. Forearm.*—In the hypertensive group, sixty-eight measurements were made upon thirty-seven subjects; the average

\*Venous bed includes veins, venules, and capillaries, i.e., vessels which cannot contract against an internal pressure of 70 to 80 mm. Hg and do not materially contribute to the peripheral resistance.

†We wish to express our thanks to Riedel-de Haen, Inc., who supplied this drug.

blood flow for the entire series was 2.86 c.c. per minute per 100 c.c. of limb volume, with a standard deviation of 1.2, and a standard error of the mean of 0.14 (Table I). In the normal group, 131 forearm measurements were made upon fifty-six subjects; the average for the entire group was 1.77 c.c. per minute per 100 c.c. of limb volume, with a standard deviation of 0.7 and a standard error of the mean of 0.06. The difference between the averages of these two groups is 1.09, and the standard error of this difference\* is 0.15, giving it a reliability† of 7.1. The reliability of a difference must be at least as high as 3.0 to rule out the possibility that chance alone may have produced it. The difference between our means for normal and hypertensive patients has so high a reliability, however, that the likelihood of failing to find the same type of relationship on repetition of our experiments is less than one in a billion, statistically. It can therefore be stated definitely that the forearm mean blood flow of hypertensive patients is greater than that of normal persons.

TABLE I

RESTING BLOOD FLOW IN VARIOUS VASCULAR BEDS OF NORMAL AND HYPERTENSIVE SUBJECTS

|              | NO. OF<br>SUBJECTS | NO. OF<br>TRIALS | MEAN<br>BLOOD<br>FLOW | $\sigma$ | $\sigma M$ | RELIABILITY OF<br>DIFFERENCE OF<br>MEANS |
|--------------|--------------------|------------------|-----------------------|----------|------------|--|
| Forearm      |                    |                  |                       |          |            |  |
| Normal       | 56                 | 131              | 1.77                  | 0.7      | 0.06       | 7.1                                      |
| Hypertension | 37                 | 68               | 2.86                  | 1.2      | 0.14       |  |
| Leg          |                    |                  |                       |          |            |  |
| Normal       | 28                 | 54               | 1.38                  | 0.5      | 0.07       | 5.5                                      |
| Hypertension | 30                 | 33               | 2.38                  | 1.0      | 0.17       |  |
| Hand         |                    |                  |                       |          |            |  |
| Normal       | 61                 | 139              | 9.32                  | 2.1      | 0.18       | 8.6                                      |
| Hypertension | 32                 | 35               | 5.38                  | 2.2      | 0.42       |  |

All blood flow figures expressed in cubic centimeters per minute per 100 c.c. of limb volume.

$\sigma$ , Standard deviation;  $\sigma m$ , standard error of the mean.

The data for the forearm are graphically represented in Fig. 1, which shows the percentage of subjects who fell into each category of blood flow readings. Approximately 11 per cent of the normal subjects, but no hypertensive patients, fell into the lowest blood flow category of 0.5 to 1.0 c.c. The highest percentage of normal subjects (45 per cent) fell within the next group, but only 14 per cent of the hypertensive patients. In the 1.7 to 2.2 c.c. range, the percentage of cases was approximately the same in both groups, and, from this point on, the initial tendency was reversed, i.e., the hypertensive subjects predominated,

\*Standard error of difference between means is derived from the formula:

$$\sigma m_1 - m_2 = \sqrt{(\sigma m_1)^2 + (\sigma m_2)^2}$$

†The reliability of the difference between two means is derived from the formula:

$$\text{Reliability of difference between means} = \frac{m_1 - m_2}{\sigma m_1 - m_2}$$

with very few normal subjects in the higher categories. In other words, there was a significant shift among the hypertensive subjects toward the greater blood flow values, although the higher normal and lower hypertensive ranges did overlap.

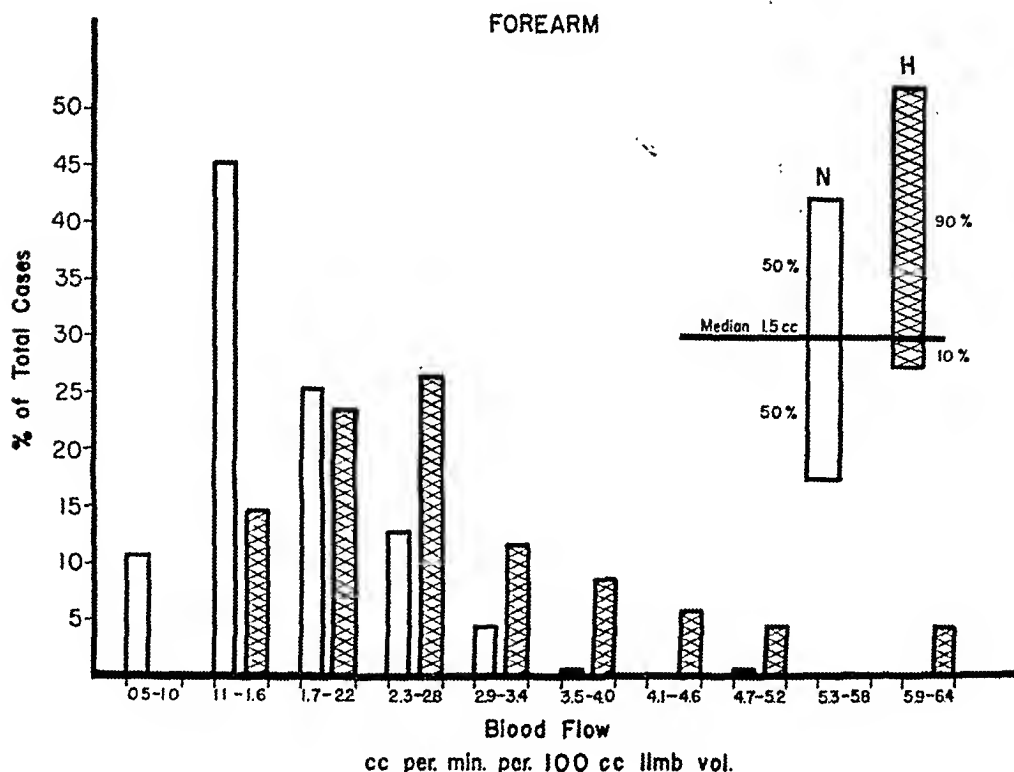


Fig. 1.—Distribution of blood flow readings in the forearms of normal (open column) and hypertensive (cross-hatched column) subjects.

These results are presented in a different fashion in Fig. 1 by relating them to the median\* of the normal series. In the hypertensive group, 90 per cent of the forearm blood flow values were greater than, and only 10 per cent were less than, 1.5 c.c., which was the median of the normal series.

*Leg.*—Table I reveals that, as in the case of the forearm, the resting blood flow in the leg in the hypertensive group was significantly higher than that in the normal series; the reliability of the difference between the two means was 5.5. Graphically (Fig. 2), the distribution of the cases was found to be similar to that observed for the forearm (Fig. 1); an overlapping of higher normal and lower hypertensive ranges was also present.

*Hand.*—Because of the fact that marked vasomotor control is known to exist in the blood vessels in the hand, it was thought of interest to study the circulation in this site (Table I). Although only thirty-five measurements were made on hypertensive patients, as compared with

\*By definition, a median is that figure which divides the cases so that exactly 50 per cent fall on either side of it.

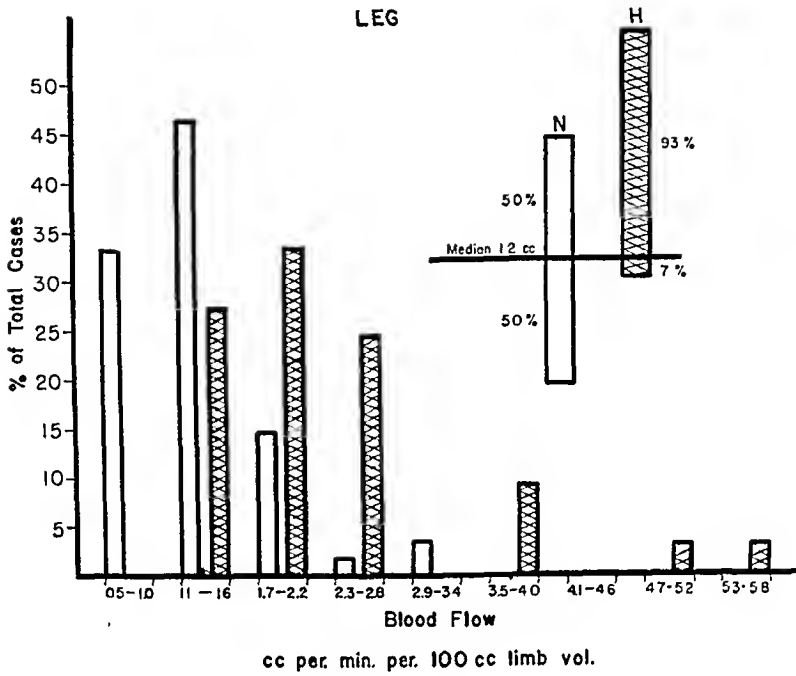


Fig. 2.—Distribution of blood flow readings in the legs of normal (open column) and hypertensive (cross-hatched column) subjects.

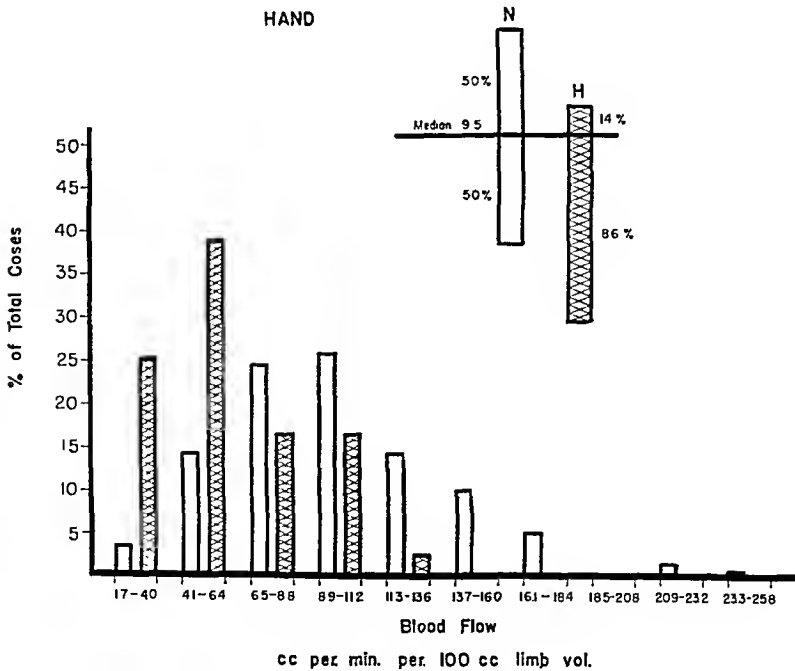


Fig. 3.—Distribution of blood flow readings in the hands of normal (open column) and hypertensive (cross-hatched column) subjects.



139 on normal subjects, the number was sufficient to indicate that the blood flow in the hand in the hypertensive group, in contrast with the forearm and leg, was significantly less than that in the normal group; the reliability of the difference between the two means was 8.6. These results are in accord with the calorimetric observations of Sheard and his associates.<sup>16</sup>

The results for the hand are graphically presented in Fig. 3. As is apparent, there is a definite tendency for the hypertensive series to shift toward the smaller blood flow ranges. The same type of relationship was evident when the data were related to the median of the control series (Fig. 3, right upper corner); 86 per cent of the hypertensive blood flows were less than, and only 14 per cent greater than, this value.

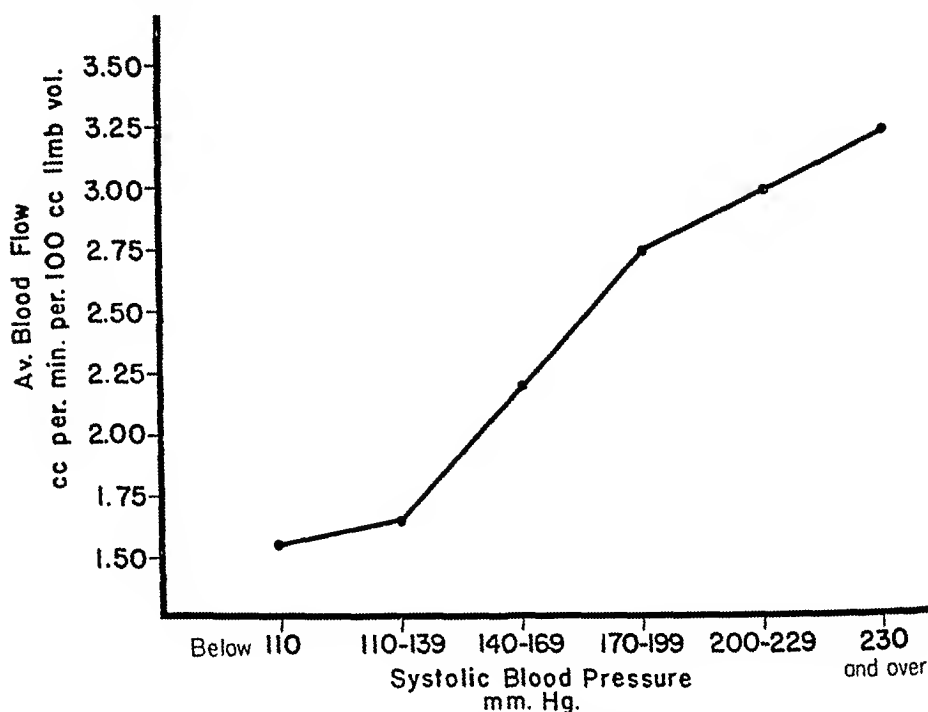


Fig. 4.—Illustrating the relationship between average forearm blood flow and systolic blood pressure for both normal and hypertensive subjects. Points represent average blood flow for each blood pressure range (coefficient of correlation =  $0.65 \pm 0.03$ ).

*Comparison of Rate of Resting Blood Flow and Height of Blood Pressure.*—The question naturally arises as to whether there is any relationship between the rate of resting blood flow and the height of the blood pressure. In order to throw some light on this point, all forearm blood flow figures in both the normal and hypertensive groups were correlated with the blood pressure. The correlation coefficient between resting forearm blood flow and systolic blood pressure was  $0.65 \pm 0.03$ , indicating that there is a marked relationship between these two factors. Since diastolic pressure has great significance in its own right, blood flow was correlated with it as well; the resulting coefficient was  $0.39 \pm 0.05$ . This figure is lower than that for systolic pressure, indicating a less marked

relationship. The pulse pressure and blood flow were likewise correlated, and the coefficient was  $0.64 \pm 0.03$ , which is practically the same as that for systolic pressure.

Fig. 4 illustrates the significance of the coefficient of correlation. In it are plotted the average forearm blood flow figures of all subjects who fell within certain ranges of systolic blood pressure. It is apparent that the average forearm blood flow rises significantly with increases in blood pressure. The correlation coefficient of 0.65, as stated above, is a statistical measure of this trend.

Since age and hypertension are associated factors, the question of the extent to which age affects the relationship between blood flow and blood pressure becomes extremely important. In order to clarify this issue the technique of partial correlation was utilized. In effect, this procedure determined what the correlation would have been if all of the subjects had been of the same age. Applied to our data, the partial correlation between forearm blood flow and systolic blood pressure, with age held constant, was 0.57. Since the original correlation was 0.65, it can be seen that holding the age constant has altered the correlation very little. In other words, age, per se, is not a factor of any consequence in producing the relationship between blood flow and blood pressure.

*Response to Local Anoxemia.*—The effect of arterial occlusion was studied on twenty-two hypertensive patients; the data obtained in a previous investigation<sup>13</sup> were used as controls. In this latter study, which was performed on twenty-six normal subjects, it was found that the average blood flow repayment in the forearm was 1.48 c.c. per 100 c.c. of limb volume per minute of arterial occlusion, with a standard deviation of 0.3 and a standard error of the mean of 0.06. In the hypertensive subjects, who were tested under similar conditions, the average repayment in the forearm was 1.56 c.c. per 100 c.c. of limb volume per minute of arterial occlusion; the standard deviation was 0.7 and the standard error of the mean, 0.14. The reliability of the difference between the means of the hypertensive and normal groups was 0.5, indicating that there is no significant difference in response to local anoxemia between the two. Further, the magnitude of the maximal single blood flow reading during the period of reactive hyperemia was no greater for the hypertensive than for the normal subject.

*Response to a Period of Exercise.*—Tables II and III reveal that considerable individual variation in repayment to exercise was present in both hypertensive and normal groups. This can probably still be attributed to differences in general physical training, despite the fact that debilitated hypertensive patients had been eliminated from the series. The important fact brought out by the procedure, was, however, that, with one exception (S. E.),\* the blood flow repayment consequent to

\*A case of chronic nephritis; diagnosis subsequently was proved at necropsy.

exercise was of approximately the same magnitude in both types of subjects. Further, no apparent difference existed in the magnitude of the maximal single blood flow reading elicited by the exercise, or in the duration of the total period of blood flow repayment.

TABLE II

## EFFECT OF EXERCISE ON BLOOD FLOW IN THE FOREARM OF NORMAL SUBJECTS

| SUBJECT | REPAYMENT* | MAXIMUM RESPONSE† | TIME OF MAXIMUM RESPONSE (SEC.) | DURATION OF REPAYMENT (MIN.) |
|---------|------------|-------------------|---------------------------------|------------------------------|
| L. B.   | 38.3       | 9.1               | 15                              | 13                           |
| A. F.   | 26.5       | 7.3               | 30                              | 14                           |
| N. N.   | 19.5       | 8.0               | 30                              | 7                            |
| R. H.   | 47.0       | 11.6              | 40                              | 14                           |
| M. W.   | 19.9       | 8.4               | 15                              | 15                           |
| A. S.   | 23.4       | 7.0               | 25                              | 12.5                         |
| A. F.   | 28.5       | 7.9               | 10                              | 15                           |
| B. W.   | 45.2       | 12.6              | 10                              | 12                           |

\*Expressed in cubic centimeters per 100 c.c. of limb volume.

†Expressed in cubic centimeters per minute per 100 c.c. of limb volume.

TABLE III

## EFFECT OF EXERCISE ON BLOOD FLOW IN THE FOREARM OF HYPERTENSIVE SUBJECTS

| SUBJECT | REPAYMENT* | MAXIMUM RESPONSE† | TIME OF MAXIMUM RESPONSE (SEC.) | DURATION OF REPAYMENT (MIN.) |
|---------|------------|-------------------|---------------------------------|------------------------------|
| C. J.   | 20.6       | 7.9               | 30                              | 17                           |
| M. G.   | 25.0       | 12.7              | 25                              | 9                            |
| S. E.   | 116.1      | 18.9              | 30                              | 23                           |
| A. M.   | 27.4       | 13.2              | 20                              | 12                           |
| M. H.   | 20.4       | 8.2               | 10                              | 9                            |
| M. B.   | 33.8       | 6.1               | 15                              | 13                           |
| G. S.   | 34.6       | 10.1              | 20                              | 12.5                         |
| L. A.   | 16.1       | 7.8               | 30                              | 10.5                         |
| B. W.   | 40.8       | 9.6               | 35                              | 17                           |
| B. B.   | 33.3       | 11.1              | 25                              | 14.5                         |
| S. B.   | 35.3       | 11.2              | 25                              | 12.5                         |
| A. P.   | 38.4       | 9.9               | 25                              | 14                           |
| M. S.   | 46.2       | 15.4              | 20                              | 11                           |
| L. B.   | 18.3       | 8.2               | 10                              | 10                           |
| C. M.   | 47.8       | 18.0              | 10                              | 12.5                         |

\*Expressed in cubic centimeters per 100 c.c. of limb volume.

†Expressed in cubic centimeters per minute per 100 c.c. of limb volume.

*Venous Tonus.*—The rationale for the procedure used in studying venous tonus in the extremities<sup>15</sup> in hypertension is as follows: On application to the limb of an external pressure which is greater than that already existing in the venous bed, there will be a passive distension of this portion of the vascular tree. This will continue until the internal pressure rises above that in the blood pressure cuff, at which point the blood will be leaving the extremity at the same rate as it enters. On application of a greater pressure, the venous bed will again be passively distended, and a further complement of blood will remain in the limb to swell its volume; this response continues with each rise in pressure until the venous bed is no longer capable of enlarging. If hypertonus existed

in this site, the application of the pressures should produce smaller increases in limb volume, since vessels with increased tone would tend to resist the passive stretching brought about by accumulation and stasis of blood. As a result, the internal pressure would mount rapidly to and beyond the level of the external pressure, so that a proportionately smaller amount of blood would be deposited in such a venous bed, as compared with one with normal tonus. Since the possibility exists that high internal pressures might be sufficient to overcome an existing venous hypertonus, only the data obtained with the lower pressures would be of value in this respect.

TABLE IV

VENOUS CAPACITY IN THE FOREARMS AND LEGS OF NORMAL AND HYPERTENSIVE SUBJECTS

|              | NO. OF<br>SUBJECTS | CUFF PRESSURE (MM. HG) |      |      |      |      |      |      |
|--------------|--------------------|------------------------|------|------|------|------|------|------|
|              |                    | 10                     | 20   | 30   | 40   | 50   | 60   | 70   |
| Forearm      |                    |                        |      |      |      |      |      |      |
| Normal       | 14                 | 0                      | 0.10 | 0.35 | 0.50 | 0.42 | 0.47 | 0.45 |
| Hypertension | 21                 | 0                      | 0.16 | 0.45 | 0.46 | 0.44 | 0.45 | 0.52 |
| Leg          |                    |                        |      |      |      |      |      |      |
| Normal       | 15                 | 0.04                   | 0.15 | 0.24 | 0.41 | 0.44 | 0.44 | 0.62 |
| Hypertension | 19                 | 0.03                   | 0.14 | 0.23 | 0.33 | 0.34 | 0.33 | 0.51 |

Figures represent the average increase in extremity volume, expressed in cubic centimeters per 100 c.c. limb volume, obtained with each successive application of 10 mm. Hg pressure, in the range from 0 to 70 mm. Hg.

Table IV reveals that there was no significant difference between the hypertensive and normal groups in the progressive volume changes elicited by the application of increasing external pressures to either the forearm or leg. These observations are compatible with the view that in hypertension the venous bed in the extremities is not in a state of increased tonus.

#### DISCUSSION

In the elucidation of the hemodynamics of hypertension, data based on the measurement of blood flow in the extremities quite properly play an important role. On the premise that the cardiac output is not increased in hypertension, and that the elevated blood pressure results from an exaggerated peripheral resistance, such studies can be of help in ascertaining the relative distribution of the hypertonus.

If a generalized and uniform vasoconstriction were present, the rate of blood flow throughout the body would be the same as that in normal subjects; the augmented pressure would be dissipated in overcoming the added resistance to the flow of blood through the arterioles. Conversely, if the hypertonus were localized (relatively or absolutely), the compensatory increase in the head of pressure, due to an augmented force of cardiac contraction, would produce a more rapid rate of blood flow through those remaining portions in which the caliber of the blood

vessels was normal. Furthermore, this increase in blood flow would vary directly with the increased height of pressure, in accordance with Poiseuille's law.

The observation in the present investigation that there is a significantly greater blood flow through the forearms and legs of hypertensive patients than in those of normal subjects would therefore be opposed to the prevailing view that the vasoconstriction which produces hypertension is evenly distributed throughout the splanchnic region and the extremities.<sup>11, 17</sup> In fact, the data lend definite support to the alternate hypothesis that the hypertonus is not uniform, for they indicate that the blood vessels of the forearm and leg share little, if at all, in the increased peripheral resistance. The observation that a high correlation exists between the magnitude of forearm blood flow and such factors as the height of systolic blood pressure, the height of diastolic blood pressure, and the magnitude of the pulse pressure would be in accord with this view. Finally, the fact that such vasodilating agents as local anoxemia and exercise elicited the same type of response in both hypertensive and normal subjects would indicate that the tonus of the vessels of the forearm in the two groups was alike. The identical results of other investigators,<sup>7, 8, 11</sup> who favor the opposite concept, can be re-interpreted in a similar manner.

However, since it cannot be stated with absolute certainty that the augmented blood flow through the forearm and leg in hypertension is the resultant solely of an increase in tonus elsewhere in the vascular bed, it may be that other methods will have to be utilized before conclusions of a final nature can be made on this subject.

It is of interest to speculate as to why the average resting blood flow in the hands of hypertensive patients was significantly less than that in the control series, whereas the reverse was true for the forearm and leg. The fact that the hand is composed principally of skin, with its numerous arteriovenous shunts, whereas, in the forearm and leg, muscle tissue predominates, may in some way explain the different responses of the two types of vascular beds. As already stated, the blood vessels of the hand are under the control of the vasomotor center, but those in the forearm and probably the leg are little, if at all, affected by vasoconstrictor impulses.<sup>9</sup> Hence, the various psychic stimuli attendant upon the introduction of a lay subject into the environment of a laboratory would tend to decrease blood flow through the hand. In view of the generally accepted fact that the blood pressure rise consequent to the application of noxious agents is much greater in the hypertensive than in the control subject, the possibility suggests itself that the low hand flow observed in the hypertensive patients was the result of an exaggerated response to the psychic stimuli associated with the procedure. Nevertheless, the other possibility, that in hypertension the nervous vasoconstrictor tonus in the blood vessels of the hand is increased, can by no means be ignored.

## SUMMARY

1. The rate of resting blood flow was studied in a series of seventy hypertensive and ninety normal subjects by means of the venous occlusion plethysmographic method.

2. It was found that in the hypertensive patients the resting blood flow in the forearm and leg was significantly greater than that in the normal group.

3. In the hand, however, the average blood flow was much less in the hypertensive than in the control subjects.

4. The fact that the blood vessels in the hand are under the control of the vasomotor center, whereas those in the forearm and leg are little, if at all, affected by vasoconstrictor impulses, was considered significant in this respect.

5. A period of local anoxemia was found to elicit a response of equal magnitude in both the hypertensive and the normal subject.

6. Similarly, the blood flow repayment after a specified amount of work was the same in the two groups.

7. Evidence was obtained which suggested that the venous bed in the extremities in hypertension is in a state of normal tonus.

## CONCLUSIONS

These observations are in direct contradiction to the prevailing theory that there is a generalized and uniformly increased peripheral resistance in hypertension. On the premise that cardiac output is not increased, most of the available data would be compatible with the view that the tonus of the blood vessels of the forearm and leg is either normal or only slightly altered.

The authors wish to acknowledge the generous cooperation of Dr. A. N. Franzblau.

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#### DISCUSSION

DR. J. MURRAY STEELE, New York, N. Y.—There is a question whether or not loss of heat to the surrounding medium does not have a good deal more to do with flow through the superficial vessels of the skin than it does with that of the muscles and the deeper vessels of the forearm.

DR. LOUIS KATZ, Chicago.—Dr. Landowne, in my department, has been studying peripheral blood flow with the leg-foot plethysmograph of Abramson and has analyzed, among other things, the flow in a number of hypertensive patients. We found that the maximal flow after reactive hyperemia is usually normal; only on a few occasions did we find a maximal flow that was greater than normal. I should like to ask Dr. Abramson if he found that the maximal flows in reactive hyperemia in the forearm or leg, exclusive of the hand or foot, were greater than, the same as, or less than, the normal maximal flow. I believe that the use of such maximal flows would be a better indicator than resting flows of the presence of permanent irreversible changes in the state of those vessels, for resting flows depend upon a variety of other influences.

Further, I should like to ask him whether he has any information to help ascertain whether the differences in resting flow which he observed in different patients depended upon the duration of the hypertension or its etiological background.

DR. IRVINE PAGE, Indianapolis, Ind.—I believe there is a moral to be drawn from this discussion, and that is that people who are working with hypertension tend toward extremes, as you doubtless all recognize.

Four or five years ago, with the announcement of Prinzmetal and Pickering's work, there was a violent reaction against the nervous system, and the splanchnic area, especially, lost caste at a most alarming rate. On second thought, it did look as though the splanchnic area was an important vascular area, and that we had gone too far in minimizing its importance. The splanchnic area is now coming back into its old place again.

DR. WILLIAM S. COLLENS, Brooklyn, N. Y.—Regarding the plethysmograph, one must immediately question the reliability of this indirect method for the measurement of blood flow through a limb. Those of you who have had experience with the plethysmograph will agree with me that certain artifacts will frequently appear which may greatly mislead the observer. Dr. Abramson himself recently published a series of artifacts in plethysmographic determinations which, if used for physiologic interpretation, would lead to erroneous conclusions. I have been impressed and annoyed with this troublesome problem in my own plethysmographic studies. The slightest deviation in any of the numerous steps in the technique easily results in curves of most bizarre variations. A method so easily influenced cannot be regarded as a reliable method for indirectly interpreting blood flow.

I believe it is very important for us to wait for the final conclusion regarding the rate of flow through the limbs until a more reliable method is found.

DR. CHARLES NEUMANN, New York, N. Y.—I did not understand clearly what precautions Dr. Abramson took to make sure that the patients he was studying were willing to take part in the experimental work.

I say that because in one series of hypertensive subjects in which we tried to find the time of reaction of constriction of the blood vessels after a stimulus we were able to demonstrate a marked difference from the normal. The blood vessels of hypertensive subjects reacted with constriction in only 40 per cent of the number of stimuli applied, whereas the percentage was 70 for the normal subjects. This was true for practically every one of the hypertensive subjects and every one of the normal subjects. It was not simply a question of averages.

Then we changed the entire laboratory, making it more like a bedroom, and immediately the per cent of reaction for the hypertensive group jumped from 40 to close to 70. The patients said they felt more relaxed, and apparently they did not offer as much mental or psychic resistance to the work that was being done.

Now it is a question, of course, whether the hypertensive patient is more commonly in a situation that is pleasing to him or not, but I believe that it is important to evaluate very closely the environmental conditions of any investigation upon the conscious human subject in order to know how normal or abnormal the situation presented to the patient may be.

DR. HENRY A. SCHROEDER, New York, N. Y.—The paper we have just heard should be very interesting to those who are investigating the nature of the increased peripheral resistance in arterial hypertension. For several years it has been believed that this resistance was generalized; that all arterioles throughout the body, with the exception perhaps of those in the kidney, were constricted equally. The evidence at present suggests that in many cases a humoral mechanism is involved. Attempts have been made to discover some substance which would reproduce these effects. There are several naturally occurring substances which constrict blood vessels of certain areas preferentially. If, as these papers suggest, the vascular constriction in hypertension is generalized but not equal, perhaps we should alter somewhat our point of view in a search for a pressor substance of which these effects may be the result.



DR. DAVID I. ABRAMSON, Cincinnati, Ohio.—I heartily agree with Dr. Steele's statement, and I am sure that Dr. Sheard does, too. As previously mentioned, we found that, when we studied the hand alone, we obtained a decrease in flow; Dr. Sheard found that he could draw the same conclusion in reference to his own data. Therefore, contrary to what Dr. Collens states, the results of the two investigations, using different methods, are not opposed to each other, but, in fact, each set of data supports the other, as far as the hand is concerned.

In reference to plotting diastolic blood pressure against blood flow, we have done this and find that there is a correlation between the two, although it is not so striking as in the case of systolic pressure and blood flow.

In reference to Dr. Katz' question, we did some work on the foot alone and also found that the blood flow in this region was normal or even somewhat diminished in hypertensive subjects. It might be expected that the foot would respond qualitatively like the hand, since both sites contain specialized blood vessels, the arteriovenous shunts. Therefore, the finding of a normal or low blood flow in these regions does not in any way vitiate the results that we obtained when we studied the forearm alone or the leg alone, in both of which arteriovenous shunts are absent.

As far as maximal response to reactive hyperemia is concerned, we feel that making one reading at a certain time after the release of the arterial occlusion pressure is not as reliable as obtaining the complete repayment by the construction of a graph from readings obtained every ten seconds until the blood flow returns to the normal level. However, in our procedure we also ascertained the maximal single response incidentally, and we found that it was no greater in hypertensive patients than in normal subjects. In other words, the degree of vasodilatation elicited by local anoxia was approximately the same in both.

We did not attempt to ascertain whether there was any relationship between height of blood flow and the type and duration of the hypertension, for we found that it was rather difficult at times to make clear-cut clinical diagnoses and to be sure in which of the generally accepted clinical categories a case fell.

In reference to Dr. Collens' objections (which, incidentally, seem to be perennial), obviously, one's results are significant only if the method is reliable and the data reproducible. We are quite well aware and have always been critical of any type of artifacts, and have, of course, discarded any records in which they were present. If the extremity is pushed into the machine, as mentioned by Dr. Collens, this is very readily apparent, and also when it is pulled out. As previously pointed out, Dr. Collens' other remark on the supposed difference between Dr. Sheard's and our results has no basis, for actually both sets of data lead to the same conclusions.

As far as environmental conditions are concerned, in reference to Dr. Neumann's question, we also tried to make our laboratory look as much like a bedroom as was possible under the circumstances. Further, no one was allowed to come into the room while the procedure was being carried out, and no loud conversation or noise of any sort was allowed because of the fact that the hand particularly, as well as the foot, responds markedly to all noxious stimuli by constricting. This would not apply to the forearm and leg, for the blood vessels in these sites are not under the control of the vasomotor system.

## COARCTATION OF THE AORTA IN CHILDREN

### THE SYNDROME OF CONSTRICTION OF THE ISTHMUS OF THE AORTA, WITH INVOLVEMENT OF THE ORIGIN OF THE LEFT SUBCLAVIAN ARTERY

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IT HAS been pointed out by the anatomic studies of Theremin,<sup>1</sup> Vierordt,<sup>2</sup> Bonnet,<sup>3</sup> and Evans<sup>4</sup> that the most common type of constriction of the arch of the aorta which is encountered in those who survive infancy with this lesion is an abrupt narrowing of the isthmus in the region of the aortic termination of the ductus arteriosus, or adjacent to it. The arterial trunks arising from the aorta proximal to this narrowed portion of the arch are usually dilated and widely patent. This accounts for the well-known clinical manifestation of a marked disparity between the force and strength of pulsation, with elevation of arterial pressure, in the vessels of the upper extremities as compared with the abdominal aorta and its peripheral branches.

A more uncommon and atypical form of congenital abnormality of the aortic arch consists in a narrowing of that vessel between the origins of the left carotid and the subclavian arteries; the orifices of these arterial trunks may be compromised, or the vessels themselves may be congenitally narrowed. The clinical manifestations associated with such anatomic changes are so unique that coarctation of the isthmus of the aorta, with involvement of the left subclavian artery, should be suspected as readily as the more common form.

#### REPORT OF CASES

CASE 1.—A. P., a girl, aged 8 years, was admitted to the Children's Cardiac Clinic of the hospital Dec. 19, 1933, and died at home Dec. 12, 1939. She was the seventh of eight children born in the United States of Italian parentage.

Her birth was normal, but she did not begin to walk until she was 4 years of age. The development of her teeth and nails was delayed, and it was noted that she was mentally retarded. Her progress in school was always very slow, so that at the age of 14 she was only in the fourth grade of elementary school.

She had measles and mumps at the age of 5 years. At 8 years she could climb five flights of stairs without any complaints. In this year a school physician recognized the presence of a heart lesion.

Physical examination on her first admission to the clinic revealed that she weighed 43 pounds and was 41 inches tall. Six years later, at the age of 14, she

From the Medical Division of the Montefiore Hospital for Chronic Diseases.  
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weighed 74 pounds and was 53 inches tall. That is, in a period of six years she had gained only 31 pounds in weight and 11 inches in height.

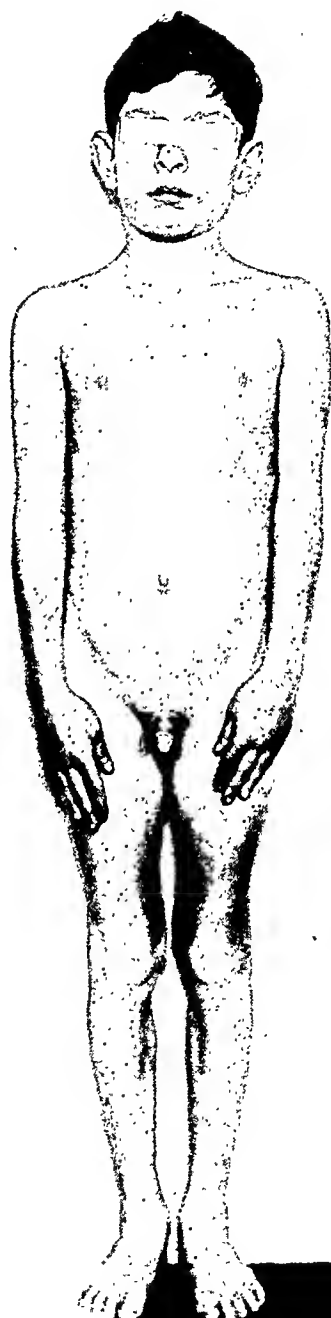


Fig. 1.—Photographs of both patients, showing overdevelopment of the right upper extremity as compared with the left upper extremity. Note that the right arm in both children is longer than the left arm. The circumferences of the right arms are likewise larger (for comparative measurements see the text).

She was a dark-complexioned girl with a head that appeared too large for her body. The right side of her face appeared fuller than the left. The right half of the chest was larger and more muscular than the left, and the right arm was 3 cm. larger in circumference than the left (Fig. 1). No pulse was palpable in the left radial, axillary, or subclavian arteries, and no pulsations were obtainable in the

abdominal or femoral vessels. There was a forceful pulsation of the arteries in the suprasternal notch, and the subclavian underneath and below the right clavicle pulsated forcibly. No blood pressure readings could be obtained in the legs.

The apical impulse of the heart was palpable in the fifth intercostal space 6 cm. to the left of the midclavicular line. A loud, blowing, systolic murmur was audible over this region, and the aortic second sound was louder than the pulmonic second sound. The lungs were free from moisture. The liver and spleen were not palpable. There was no edema of the lower extremities.



Fig. 2.—A, Roentgenogram of the heart in Case 1, in the anteroposterior view, showing marked enlargement of the left ventricle, absence of the aortic knob, aneurysmal dilatation of the supraventricular portion of the aorta, and erosion of the ribs on the right side only. B, Roentgenogram of the heart in Case 1, in the left oblique position, showing enormous aneurysmal dilatation of the supraventricular portion of the aorta and narrowing of the arch in proximity to the spinal column. Note the enlargement of the aorta immediately below the constriction.

Fluoroscopic examination of the chest revealed that the lung fields were clear. The heart showed marked enlargement of the left ventricle; the rounding occupied the lower two-thirds of the heart, and extended below the diaphragm. In the anteroposterior view the aortic knob could not be visualized. The ascending portion of the aorta was markedly dilated, and this could be best seen with the child in the left oblique position. A loss of continuity of the aortic arch could be visualized in proximity to the site of coarctation. There was slight dilatation of the aorta distal to this region.

Roentgenograms of the chest confirmed these observations, and also revealed erosion of the caudad portions of several of the ribs on the right side only (Fig. 2).

The electrocardiogram showed left axis deviation, with a negative T wave in Lead III. Complete studies of the osseous system did not reveal any significant changes. The blood Wassermann reaction was negative.

*Course and Progress.*—On Oct. 22, 1935, a diastolic murmur was audible for the first time in the region of the second intercostal space to the right of the sternum. This was transmitted to the right shoulder and was also heard well in the back, between the shoulder blades. At this time a shock could be felt over the second intercostal space to the right of the sternum; it was synchronous with the closure of the aortic valves. The blood pressure was now 140/80 mm. Hg in the right arm, but no pulse or blood pressure reading was obtainable on the left arm, abdomen, or legs.

With the progressive development of the aortic insufficiency the blood pressure in the right arm increased gradually so that, on May 31, 1938, it was 170/68 mm.

Hg. The pulse in the right arm was now collapsing in type, and the pulsations of the subclavian artery and carotid on this side were much more forceful; both of these pulsations were almost wholly absent on the left side. Her basal metabolic rate was plus 33 per cent. In the summer of this year she began to experience occasional fever, unaccompanied by joint pains. Some of these febrile periods lasted over a week, and, in the course of a few weeks, the temperature remained persistently elevated, so that she had to go to bed. She now complained of severe headache, dizziness, profuse sweating, and shortness of breath even at rest. Her mental reactions became slower and inadequate. She could not remember her birthday and failed to answer simple questions.

On Sept. 9, 1939, her spleen was palpable 3 cm. below the costal margin, and, because of the increasing malaise and fatigue, she was admitted to the wards of the hospital.

Examination on this day revealed that she was very pale. She showed a typical "café au lait" color. Her temperature was 101.2° F., her pulse rate, 128 per minute, and her respiratory rate, 28. The blood pressure in the right arm was now only 116/86 mm. Hg. The trachea was pulled slightly to the left side. The right carotid vessels pulsated forcibly, and a systolic thrill was palpable over them. On the left side the pulsations were barely visible in the carotid sheath.

Measurements of the chest showed that the distance from the spine to mid-sternum on the right side was 38 cm., and 36 cm. on the left side. The left breast was slightly higher than the right. The muscles on the right half of the back were much better developed and more voluminous than those of the left side. The right arm was 1.5 cm. longer than the left, and the circumference of the middle of the right arm was 2.75 cm. larger than that of the left. The right wrist measured 13 cm. in circumference, and the left, only 12.75 cm. The circumference and length of both legs were equal, except for the right ankle, which was 0.5 cm. larger than the left.

TABLE I

CASE 1. OSCILLOMETRIC READINGS FROM ALL FOUR EXTREMITIES

| RIGHT |    |   |    |    | MM.<br>Hg | LEFT |   |   |   |   |
|-------|----|---|----|----|-----------|------|---|---|---|---|
| A     | B  | C | D  | E  |           | A    | B | C | D | E |
| ½     | Ⅲ* | Ⅲ | Ⅲ  | 1  | 140       | ⅛    | ⅛ | 0 | 0 | 0 |
| ½     | Ⅲ  | Ⅲ | 3  | 3  | 120       | ⅛    | ⅛ | 0 | 0 | 0 |
| ½     | ½  | Ⅲ | 3½ | 3½ | 100       | ⅛    | ⅛ | Ⅲ | ½ | ¼ |
| ¾     | ½  | ¼ | 3½ | 3½ | 80        | ½    | ¼ | Ⅲ | ¾ | ¼ |
| ¼     | ¼  | Ⅲ | 1  | 1  | 60        | ¼    | ¼ | Ⅲ | ¼ | ¼ |

A, mid-thigh, normal oscillation from 6 divisions up.

B, mid-calf, normal oscillation from 4 to 6 divisions.

C, ankle, normal oscillation from 2 to 4 divisions.

D, upper arm, normal oscillation from 6 divisions up.

E, forearm, normal oscillation from 3 divisions up.

\*Barely perceptible oscillation.

The oscillometric readings showed a marked diminution in the left arm (Table I), and a marked reduction in the oscillations in both lower extremities. Repeated blood cultures revealed the *Streptococcus viridans*. The heart now beat forcibly. A systolic thrill was palpable at the aortic area. There was a loud systolic murmur which was heard best at the apical region of the heart, and a loud to-and-fro murmur at the second intercostal space to the left of the sternum which was transmitted to the apical region of the heart.

No collateral pulsations were noted on the chest wall, and again there was no palpable pulsation in the left radial artery, the abdominal aorta, or the vessels of the lower extremities.

*Comment.*—A diagnosis of coarctation of the aorta, with involvement of the left subelavian artery, was made on a girl who showed asymmetrical development of the upper half of her body. No pulses were palpable in the left subelavian, axillary, or radial arteries, and no blood pressure readings could be obtained in the left arm or the lower extremities. She developed subacute bacterial endocarditis, with aortic insufficiency, and died as a result of this complication.

CASE 2.—R. H., a boy, aged 9 years, was brought to the clinic for advice on the possibility of ligating a patent ductus arteriosus which had been recognized at the age of 3 years.

He was a premature baby, but nothing unusual was noted at birth except a murmur which was heard all over the precordium. During his first years of life, his chest was noted to bulge anteriorly on the left side. He had had the usual diseases of childhood, but had never been ill enough to warrant a long period of rest in bed.

Physical examination on Oct. 30, 1940, revealed a malnourished boy who weighed 55 pounds and was 50 inches tall. He was slightly cyanotic and showed a pasty, circumoral pallor. His face was slightly asymmetrical. The right arm measured 52 cm., and the left, 47.5 cm., from the acromioclavicular joint to the middle of the third finger. The circumference of both upper arms was 18 cm. The circumference of the right fist was 20 cm., and that of the left was 19 cm. (Fig. 1).

The right carotid, axillary, and radial arteries were definitely palpable. The left carotid artery was barely palpable, but the left axillary, brachial, and radial arteries were not palpable at all. No pulsations were felt over the abdominal aorta, and the pulsations over both femorals were markedly diminished.

He had a marked deformity of the chest in the region of the left half of the sternum and the second, third, fourth, and fifth costosternal junctions, with no abnormal curvature of the spine. The superficial veins of the chest were dilated on both sides anteriorly. There was a heaving impulse, systolic in time, extending from the second to the fourth left intercostal spaces in the midclavicular line. Closure of the pulmonic valves was palpable within the nipple line. Over that region, a very loud "machinery" murmur was heard best at the second intercostal space to the left of the sternum. The pulmonic second sound was markedly accentuated. The diastolic element of the murmur was transmitted to the level of the third intercostal space, and the systolic element, to the left of the sternum as far up as the left clavicle. No murmurs were audible posteriorly.

The blood pressure in the right arm was extremely variable. One time it was 84/56, and at another time it was 90/68. Blood pressure readings could not be obtained from the left arm or either of the lower extremities.

The lungs were free from moisture. The liver and spleen were not palpable. There was no edema of the lower extremities.

Fluoroscopic examination of the chest revealed that the left ventricle was definitely enlarged. This enlargement was best seen with the patient in the left oblique position. In the anteroposterior view there was tremendous dilatation of the pulmonic artery, and its secondary branches pulsated so forcibly that there was a very definite "hilar fling." The supraventricular portion of the aorta could be visualized, but the tremendous dilatation of the pulmonic artery made it impossible to see the descending portion. A roentgenogram of the chest confirmed these observations (Fig. 3).

Contrast visualization of the heart and great vessels showed an indentation on the left side of the superior vena cava, with slight compression, presumably by

the pulmonic artery.\* The right auricle and right ventricle were of normal size. The intraventricular septum was convex to the right when the right ventricle was filled. The pulmonic artery showed marked dilatation from its origin to its bifurcation. The left pulmonic artery was visualized, and was perhaps slightly dilated, but not in proportion to the dilatation of the main artery. There was no evidence of a communication between the right and left ventricles. The left ventricle was normal in size. The aorta was slightly dilated at its base. It was visualized indistinctly as far as the level of the left pulmonic artery. When the aorta was visualized faintly, there was still a slight residual opacification of the pulmonic artery. A reflux into the inferior vena cava was noted during the early phase of injection.

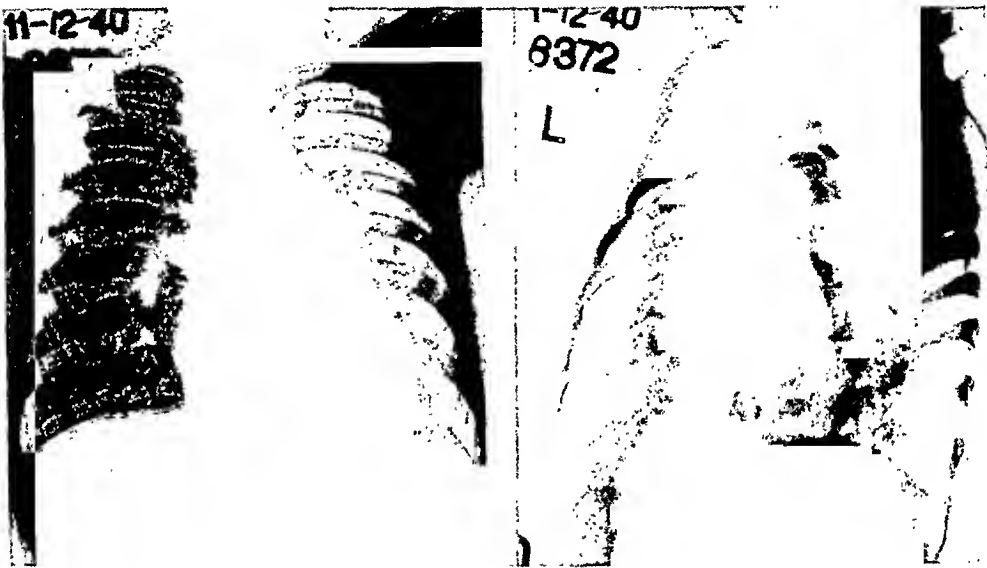


Fig. 3.—Roentgenograms in Case 2, revealing unusual dilatation of the pulmonic artery in the anteroposterior view. Note the absence of any erosion of the ribs.

TABLE II

CASE 2. OSCILLOMETRIC READINGS FROM ALL FOUR EXTREMITIES

| RIGHT |     |   |       |     | MM.<br>Hg | LEFT |     |     |     |     |
|-------|-----|---|-------|-----|-----------|------|-----|-----|-----|-----|
| A     | B   | C | D     | E   |           | A    | B   | C   | D   | E   |
| m*    | m   | m | 1/8   | 1/8 | 140       | 1/8  | 1/8 | 0   | 0   | 0   |
| 1/2   | m   | m | 1/2   | 1/2 | 120       | 1/8  | 1/4 | 1/8 | 0   | 0   |
| 1/2   | 1/8 | m | 1 1/2 | 1/2 | 100       | 1/2  | 1/2 | 1/4 | 1/2 | 1/4 |
| 1/2   | 1/4 | m | 1 1/2 | 1/2 | 80        | 1/2  | 1/2 | 1/2 | 1/4 | 1/4 |
| 1/4   | 1/4 | m | 1/2   | 1/8 | 60        | 1/4  | 1/4 | 1/4 | 1/4 | m   |

- A, mid-thigh, normal oscillation from 6 divisions up.
  - B, mid-calf, normal oscillation from 4 to 6 divisions.
  - C, ankle, normal oscillation from 2 to 4 divisions.
  - D, upper arm, normal oscillation from 6 divisions up.
  - E, forearm, normal oscillation from 3 divisions up.
- \*Barely perceptible oscillation.

The examination indicated, therefore, marked dilatation of the pulmonic artery proximal to the region of the bifurcation, with prolonged opacification. This is encountered in association with a patent ductus arteriosus. It is possible that the slight dilatation of the base of the aorta is to be interpreted as indicating a slight narrowing of the descending aorta in the region of the patent ductus.

\*We wish to thank Dr. M. L. Sussman, Director of the X-Ray Division of the Mount Sinai Hospital, New York City, for this report.

The electrocardiogram revealed right axis deviation.

The oscillometric readings revealed a markedly diminished amplitude in the left arm and both lower extremities (Table II).

Skin temperatures which were obtained at a room temperature of 65.5° F. showed a significant difference between the upper and lower extremities, as well as between the arms.

The injection of histamine produced a uniform flare in all four extremities.

The blood Wassermann reaction was negative.

*Comment.*—In the case of a boy, aged 9 years, a diagnosis of coarctation of the aorta, with involvement of the left subclavian artery, was made in the presence of a widely patent ductus arteriosus. Evidences of collateral circulation were absent. Ligation of the duct was not attempted because of the associated cardiac complications.

#### DISCUSSION

The pathology and pathogenesis of stenosis of the isthmus of the aorta have been amply discussed by Blackford,<sup>5</sup> and others, who have concluded that the constriction of the arch is a prenatal malformation, to which there is added at birth the mechanical traction resulting from closure of the ductus arteriosus. The deformities of the subclavian arteries, such as the total absence or diminution in the caliber of the vessels, or a constriction of their orifices, very likely develop at the same time as the narrowing of the arch of the aorta. From the few cases reported to date it would appear that the left subclavian artery is the one more commonly involved<sup>9-15</sup> (Table III). The occasional presence of right-sided involvement of the subclavian artery, whose site of origin from the aorta is quite a distance from the arterial insertion of the duct, as well as the persistent patency of the duct (Case 2) which is found in some cases, supports the theory of the prenatal origin of these abnormalities, independent of the traction resulting at birth from the involution of the ductus arteriosus.

Obviously, when the right subclavian artery is implicated, the clinical manifestations are the reverse of those found with coarctation of the aorta and involvement of the left subclavian artery. The increase in pressure in the collateral vessels proximal to the constriction of the aorta and the left subclavian artery results in a series of clinical phenomena that should be particularly searched for if the diagnosis of this lesion is to be established early in life.

*Asymmetry of the Body and Overgrowth of One Limb in Coarctation of the Aorta With Involvement of the Left Subclavian Artery.*—Both of these children had an asymmetrical development, with overgrowth of the muscular and bony portions of the right upper half of the thorax and right arm, together with a congenital malformation of the heart. A careful search of the more recent literature revealed exceedingly few conditions that may be responsible for such maldevelopments. Schabad<sup>16</sup>



TABLE III  
OBSERVATIONS ON REPORTED CASES OF COARCTATION OF THE AORTA, WITH IMPLICATION OF THE LEFT SUBCLAVIAN ARTERY

| HEART JOURNAL  |               |           |      |                    |                   |                |                |          |  |                        |                                      |                                 |                               |
|--|---------------|-----------|------|--------------------|-------------------|----------------|----------------|----------|--|------------------------|--------------------------------------|---------------------------------|-------------------------------|
| OBSERVATIONS ON REPORTED CASES OF COARCTATION OF THE AORTA, WITH IMPLICATION OF THE LEFT SUBCLAVIAN ARTERY |               |           |      |                    |                   |                |                |          |  |                        |                                      |                                 |                               |
| AUTHOR   | YEAR REPORTED | AGE (YR.) | SEX  | RIGHT RADIAL PULSE | LEFT RADIAL PULSE | FEMORAL PULSES | BLOOD PRESSURE |          | ROENTGEN-<br>OGRAPHIC<br>OBSERVA-<br>TIONS   | NECROPSY FINDINGS      |                                      |                                 |                               |
|  |               |           |      |                    |                   |                | RIGHT ARM      | LEFT ARM |  | AORTA                  | LEFT SUB-<br>CLAVIAN<br>ARTERY       | RIGHT SUB-<br>CLAVIAN<br>ARTERY | AORTIC VALVES                 |
| Lesseliere   | 1882          | 20        | F    | Palpable           | Feeble            | Feeble         |                |          |  | Uniform constriction   | Atrophied and obstructed by peduncle |                                 | Bicuspid valve                |
| Dencker  | 1925          | 46        | M    | Full               | Absent            | Absent         | 185/85         | 0        | Narrowing of aorta in right oblique position |                        |                                      |                                 |                               |
| Woltman and Sheldens   | 1927          | 20        | M    | Full               | Diminished        | Diminished     | 164/86         | 126/110  |  |                        |                                      |                                 |                               |
| Turkington   | 1929          | 23        | Full | Indistinct         | Absent            | Absent         | 210/110        | 130/80   |  | Constriction at ductus | Aberrant cordlike structure          |                                 | Loud blowing diastolic murmur |

|   |      |    |   |          |                    |                 |         |        |  |                                |                     |  |                   |
|---|------|----|---|----------|--------------------|-----------------|---------|--------|--|--------------------------------|---------------------|--|-------------------|
| Shatzki and<br>Haller-<br>man <sup>10</sup> | 1930 | 15 | M | Full     | Dimin-<br>ished    | Absent          | 185/140 | 135/90 | Prestenotic<br>and aneu-<br>rysmal<br>dilatation<br>in left<br>oblique<br>position |                                |                     |  |                   |
| Ratschow<br>and<br>Arendt <sup>11</sup>     | 1934 | 31 | M | Palpable | Absent             | Dimin-<br>ished | 150/65  | 80/55  | Right-sided<br>scalloping<br>of ribs<br>6 to 9                                     |                                |                     |  |                   |
| Parker and<br>Dry <sup>12</sup>             | 1938 | 26 | M | Large    | Hardly<br>palpable | Absent          | 210/40  | 100/78 | Right-sided<br>scalloping<br>of ribs   | Constric-<br>tion at<br>ductus | Abnormally<br>small |  | Bicuspid<br>valve |
| Bayley<br>and<br>Holoubek <sup>13</sup>     | 1940 | 32 | M | Forceful | Absent             | Palpable        | 154/78  | 98/78  | Right-sided<br>erosion of<br>ribs  |                                |                     |  |                   |

*Observations on Reported Cases of Coarctation of the Aorta, With Implication of the Right Subclavian Artery*

|                                  |      |    |   |  |  |  |        |        |                                     |                                 |  |  |  |
|----------------------------------|------|----|---|--|--|--|--------|--------|-------------------------------------|---------------------------------|--|--|--|
| East <sup>14</sup>               | 1932 | 44 | F |  |  |  |        |        | Constric-<br>tion below<br>the duct | Aberrant                        |  |  |  |
| Love and<br>Holmes <sup>15</sup> | 1939 | 44 | M |  |  |  | 150/90 | 210/95 | Constric-<br>tion of<br>isthmus     | Abnormal<br>origin;<br>narrowed |  |  |  |

reported a 9-year-old boy with asymmetry of the arms and intense cyanosis of the entire body who suffered from recurrent attacks of syncope and shortness of breath. The length of the right arm from the acromion process to the tip of the middle finger was 54.2 cm., and that of the left arm was 52.4 cm. The control differences in the average child were found to be only 0.2 to 5 cm. There was a large pulsation over the pulmonic artery, and a systolic murmur which was continuous with a loud diastolic murmur (machinery murmur) was audible over the chest. The blood pressure (obtained with a Riva Rocci instrument) was 83 in the right arm and 73 in the left. Sphygmograms revealed that the apex of the curve on the left was lower than that on the right. Although no mention was made of the femoral pulses in this boy, it is very likely that he had coarctation of the aorta, with a widely patent ductus, in which the orifice of the left subelavian artery was involved.

In a cyanotic infant, aged 9 months, who showed clubbing of the fingers and toes and was suspected of having a congenital heart lesion, Scott<sup>17</sup> found a nevus 1 cm. in diameter on the right shoulder. There was atrophy of the entire left side of the body, including the skull, left arm, and left leg. The fact that this child's mother had a similar hemiatrophy suggests that the condition in the infant was the result of a cerebral lesion, rather than the effect of malformation of the vessels at the base of the heart.

Chandler<sup>18</sup> described local overgrowth of the left arm, with a congenital deformity of the left hand, in a colored boy whose teleoroentgenogram revealed marked enlargement of the left side of the base of the heart in the form of an aneurysmal dilatation. Unfortunately, no mention was made of the blood pressure readings or the pulses in the lower extremities.

Chandler pointed out that arteriovenous fistulas, vascular nevi, hemangiomas, and lymphangiomas may cause overgrowth of an extremity, if there is faulty development of the vascular tree in the fourth week of embryonic life. To these may be added the overgrowth of an arm resulting from circulatory changes caused by cervical ribs. The extremity affected shows an overgrowth of all elements, and the surface of the skin has a distinct elevation of temperature. In some cases the venous pressure is increased, and hypertrophy of the heart may result. All of these conditions may be easily distinguished from coarctation of the aorta, in which there are diminished blood pressure and force and strength of the pulsations in the lower extremities.

An instance of atrophy of the left arm, with congenital heart disease, was described in a 3-week-old infant who presented a left upper extremity that had been pale and cyanotic from birth and in which the pulse could not be obtained. At necropsy there was an overriding aorta, with a defect of the membranous portion of the interventricular septum.

In the upper part of the ductus there was a thrombus which extended into the ascending aorta, and into the lumen of the left common carotid, subclavian, axillary, and brachial arteries.<sup>19</sup>

*The Blood Pressure in Coarctation of the Aorta, With Special Reference to the Differences in the Arms.*—The elevation of the arterial blood pressure in the arms, as contrasted with the absent, diminished, or lowered arterial blood pressure in the femoral arteries, has been emphasized as a sign associated with coarctation of the aorta. From a study of this subject, King<sup>20</sup> has suggested a modification of the general opinion that the presence of hypertension affords the most important clue to isthmus stenosis. In a review of the blood pressure readings in all the cases of coarctation of the aorta reported between 1892 and 1936 in which such records were obtainable, he found 146 cases in which there were definite hypertension in one or both arms and a comparatively lower pressure, with feeble pulsations, in the legs. In fifty-six of these cases the average pressure in the right arm was found to be 190/92, and that in the left arm, 185/94. Such slight differences in the pressure in the arms have been noted in previous reports, and have been attributed to a slowing of the blood stream as it passes the mouth of the left subclavian artery when there is a narrowing of the aorta distal to it.

In ten other cases, however, five of which have been mentioned above, and in those of Amberg,<sup>21</sup> Hersdoffer,<sup>22</sup> and Villafane and Menendez,<sup>23</sup> King called attention to a wider difference in the blood pressure in the arms; that in the left arm was substantially lower than that in the right. Similar observations were reported recently by Borgard<sup>24</sup> and Hills<sup>25</sup> in two cases of coarctation of the aorta. The suggestion has been offered by the latter observers that such radial differences in the blood pressure in the arms must inevitably be the result of a constriction or obstruction of the orifice of the left subclavian artery. The total absence of a blood pressure reading in the left arms of the two children reported in this study lends further support to this contention.

*The Disparity in the Strength and Force of the Pulsations of the Two Radial Arteries.*—A difference in the size and force of the pulsations in the two radial arteries was regarded by the older clinicians as a sign of coarctation of the aorta, but only a few considered this as evidence that the constriction of the isthmus also involved the origin of the left subclavian artery. Erman<sup>26</sup> noted this difference in a 19-year-old boy who developed a left-sided hemiplegia. On some days the left radial pulse would be totally absent, but pulsations could be felt in the left brachial artery. However, at necropsy the diameters of both subclavian orifices were found to be the same. In Schichold's<sup>27</sup> 32-year-old servant girl, the left pulse was not only smaller than the right, but was also observed to lag behind the femoral pulsations, yet necropsy revealed that the orifice of the left subclavian artery was larger than the right. Hochsinger<sup>28</sup> suspected coarctation of the isthmus in a 13-year-old boy who

had no femoral pulsations, but showed marked pulsations of the right subclavian and the left carotid arteries, and a left radial pulse which was half as large as the right.

Brown<sup>29</sup> diagnosed congenital stenosis of the aorta in a man, aged 27 years, in whom he thought the abnormality in some way involved the orifice of the left subclavian artery, for the right subclavian artery was large and pulsated forcibly, whereas the left was extremely small and its pulsations were very faint. In Stürsberg's<sup>30</sup> patient, the pulsations of the left subclavian, brachial, and radial arteries were smaller than those on the right side. The blood pressure (obtained with a Riva Roci instrument) was 102 in the right arm and 77 in the left. In slow sphygmographic curves he was able to demonstrate that there was no actual delay of the ascending limb of the radial pulse in the left arm, as compared with that in the right, but that the apex of the pulse was weak, blunt, and retarded in the left radial; the occurrence of this phenomenon was confirmed by King<sup>31</sup> in his excellent study of the subject. The lagging of the left radial pulse, when it is diminished in force and volume, appears to be synchronous with that of the femorals. King felt that this distinct difference in the pulsations of the two radial arteries in patients with coarctation of the aorta was the result of the proximity of the orifice of the left subclavian to the narrowed portion of the isthmus. The momentary slowing of the blood stream in the aorta as a result of the stricture causes slow passage of blood over the orifice of the left subclavian artery, and this produces the type of pulse tracings described.

In the light of more recent observations, however, it must be conceded that, in some patients with coarctation of the aorta, an actual diminution of the volume of blood flow in the left subclavian artery causes the pulse differences in the two arms. Nevertheless, this sign in itself, although very suggestive, cannot be taken as a criterion of involvement of the orifice of the subclavian artery because of the inconsistent necropsy observations.

*Differences in the Force and Strength of Pulsation Between the Upper and Lower Extremities.*—A recent summary of all the cases of children with coarctation of the aorta which have been reported to date convinced Eisenberg<sup>32</sup> that a disparity of force and strength of pulsation between the radial arteries and the abdominal and femoral vessels is of the greatest importance in the recognition of a narrowing of the isthmus, no matter what accompanying conditions may be present in the heart. Hamilton and Abbott<sup>33</sup> considered retardation and diminution, or even absence to the palpating finger, of the femoral pulse as pathognomonic of coarctation. They pointed out, however, that in adults this sign may not be constant, either as to its presence or as to the extent of the diminution, which seems to bear no relationship to the degree of stenosis. Uniform diminution of the oscillographic readings in both

lower extremities, as compared with the upper limbs, is of greater value when there is doubt about the diagnosis in children.

*The Roentgenologic Diagnosis of Coarctation of the Aorta Involving the Orifice of the Left Subclavian Artery.*—In children with coarctation of the aorta, a superficial collateral circulation over the back, such as is found in adults, is seen only rarely. However, an internal collateral circulation must certainly exist, and evidence of this may at times be detected in roentgenograms of the chest (Fig. 2). This consists of erosion along the lower margins of the ribs posteriorly, usually on both sides of the chest. The defects may be multiple, affecting more than one rib, and not infrequently may produce multiple defects in the same rib.<sup>34</sup>

In patients with coarctation of the aorta involving the left subclavian artery, the erosion of the ribs, when present, is found on the right side only. The extent of the rib erosion in such cases will depend on the degree of constriction of both the aorta and the left subclavian artery, in the *absence* of a widely patent ductus arteriosus. This accounts for the absence of rib erosion in our second case.

Other roentgenologic evidences that may be of help in the recognition of coarctation of the aorta are absence of the aortic knob in the antero-posterior view, a prestenotic aneurysmal dilatation of the aorta proximal to the constriction, dilatation of the aorta distal to the narrowing, and failure to visualize the aortic continuity in the left oblique position. Often, in this position, there is an actual absence of the aortic shadow where it narrows down, so that it cannot be seen at all in that region (Fig. 3).

Enlargement of either the left or right ventricle will depend more on the accompanying valvular lesion than on constriction of the arch. A large left ventricle may be expected with aortic insufficiency, which is usually due to infection of a bicuspid valve (found in 25 per cent of cases) with the *Streptococcus viridans*. Enlargement of the right ventricle occurs when the ductus arteriosus is widely patent. At times a fullness in the right hilar region, with a more pronounced dilatation of the vessels on the right side, may help to detect obstruction of the left subclavian artery.

The likelihood that diodrast studies can delineate the subclavian arteries should be thought of when searching for absence of the vessel, for a large subclavian artery on the left side may be easily visualized with this method.<sup>35</sup>

#### SUMMARY AND CONCLUSIONS

The clinical signs associated with coarctation of the aorta which involved the origin of the left subclavian artery were studied in two children.



Both children had an asymmetrical development of the upper half of the body; the right half of the chest was larger than the left, and the right upper arm was longer, and larger in circumference, than the left.

Both children had no pulsations in the left axillary, brachial, and radial arteries. At times they had a diminished pulsation of the left carotid artery.

The blood pressure was obtainable in the right arm only. It was elevated in one child and within normal limits in the other.

In one child with aortic insufficiency, a roentgenogram of the chest revealed sulci and grooves in the caudad portions of the posterior portions of the ribs on the right side only. In the second child, who had a widely patent ductus arteriosus, there was no collateral circulation.

The pulsations of the abdominal and femoral vessels were absent, or retarded, or diminished in volume, and this was confirmed by oscillographic readings.

Coarctation of the aorta, with involvement of the orifice of the left subclavian artery, should be easily suspected in the presence of such abnormalities.

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## AN IMPROVED BLOOD PRESSURE CUFF

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IT HAS undoubtedly been the experience of every man in clinical practice that, in taking a blood pressure reading, especially on obese persons with large arms, the cuff has a tendency to slip out and "herniate" from the restraining binder as it is progressively inflated. The

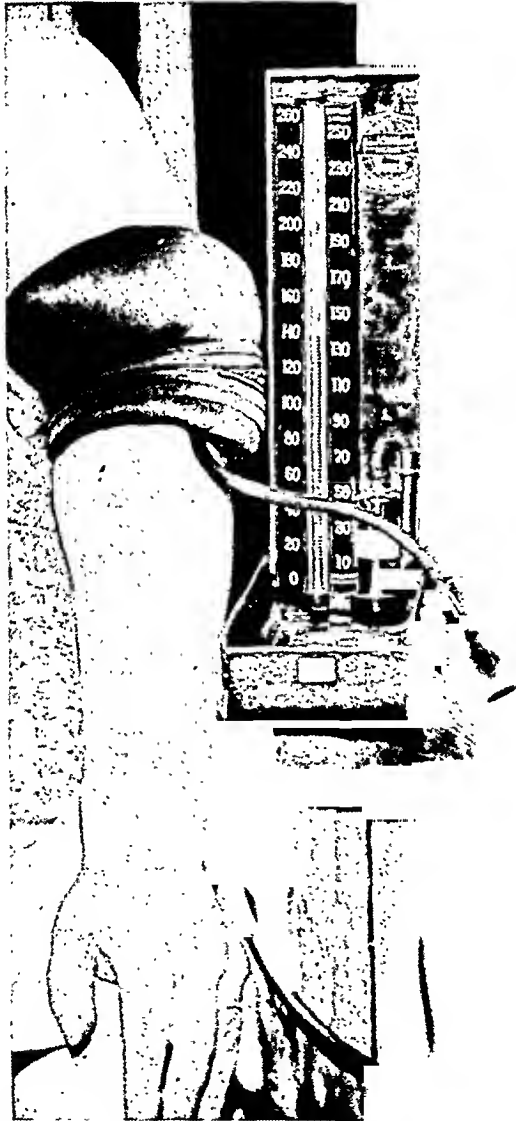


Fig. 1.—Standard blood pressure cuff inflated on stout arm, showing "herniation" and slipping of cuff.

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restraining binder then acts as a cordlike band which frequently produces pain at the site of constriction. The herniation of the rubber bag and the pain are factors in producing false readings.

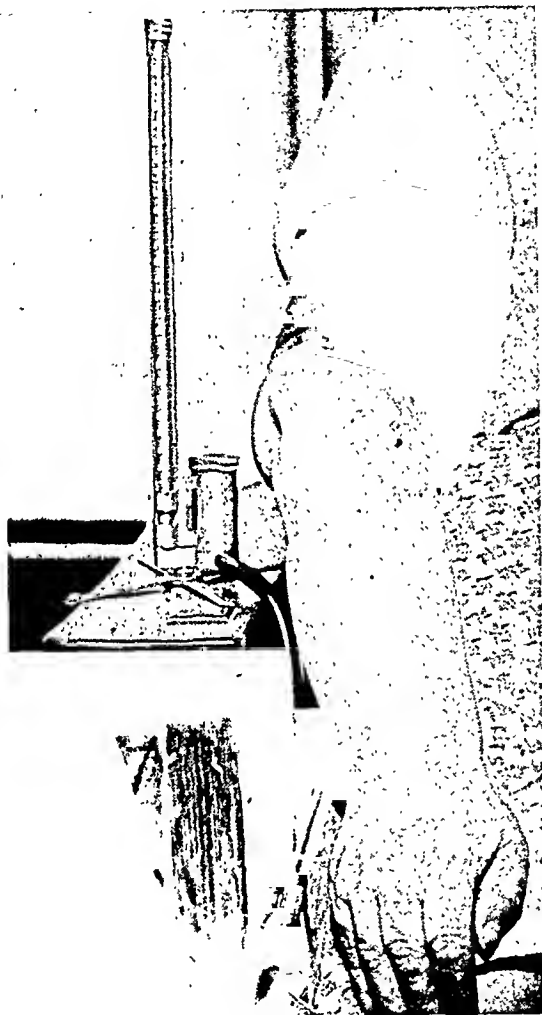


Fig. 2.—Improved cuff with same degree of inflation.

We have devised a cuff which eliminates this difficulty. The rubber bag is constructed in such a fashion that its outer wall is inelastic. The physician can easily improve the ordinary cuff which he is at present employing by cementing a piece of canvas to the outer portion of the rubber bag, thus destroying its elasticity. Blood pressure measurements made with the new cuff and with the old type, when no herniation occurs, have been found to be identical. We have arranged with a manufacturer\* to market this improved cuff at the same price as that of the present standard cuff.

# A DEVICE FOR OBTAINING ELECTROCARDIOGRAPHIC LEADS FROM THE PRECORDIUM

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**A**N INSTRUMENT was devised to obtain precordial leads by the various recommended methods, as well as the standard leads, without changing lead wires or electrodes during the process. It has been arranged so that several patients may be connected in succession to a single electrocardiograph at a rapid rate, as may be required in certain investigations or in the examination of large groups.

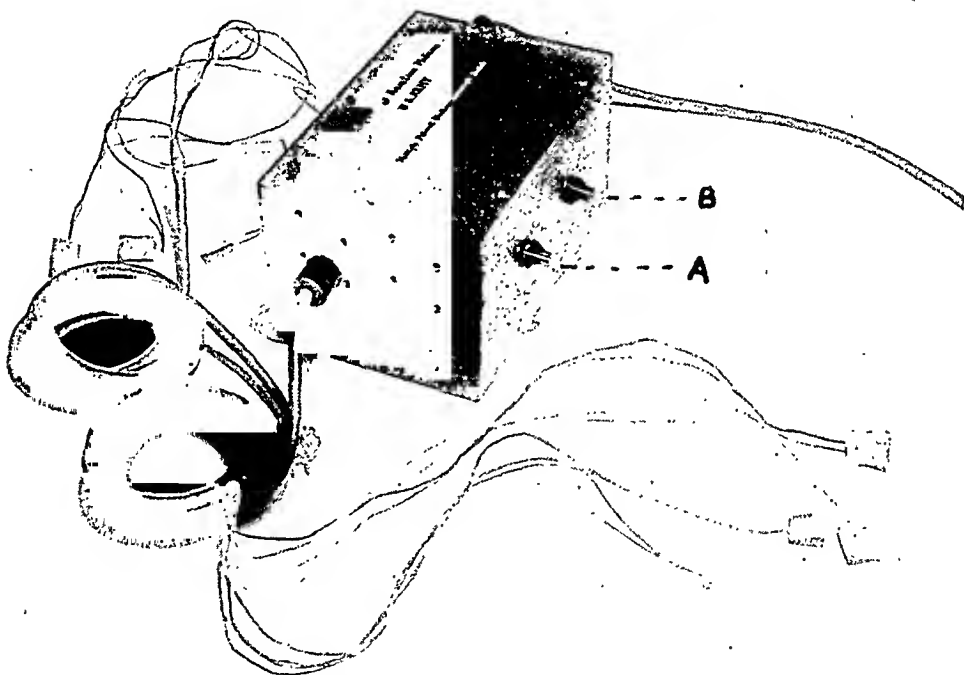


Fig. 1.—Exterior view of multiple patient-switch box. A, Patient selector switch; B, Lead selector switch.

## DESCRIPTION OF DEVICE

To each patient four electrodes are attached—three to the usual extremities and one to the precordium. Each electrode is connected to a prong of a four-prong polarized plug by a four-conductor cable. Any number of patients (in this case, four) may be so connected. Each plug is inserted into a polarized jack on the left-hand side of the switch box. This switch box has two control switches. The

From the School of Aviation Medicine, Randolph Field, Texas.  
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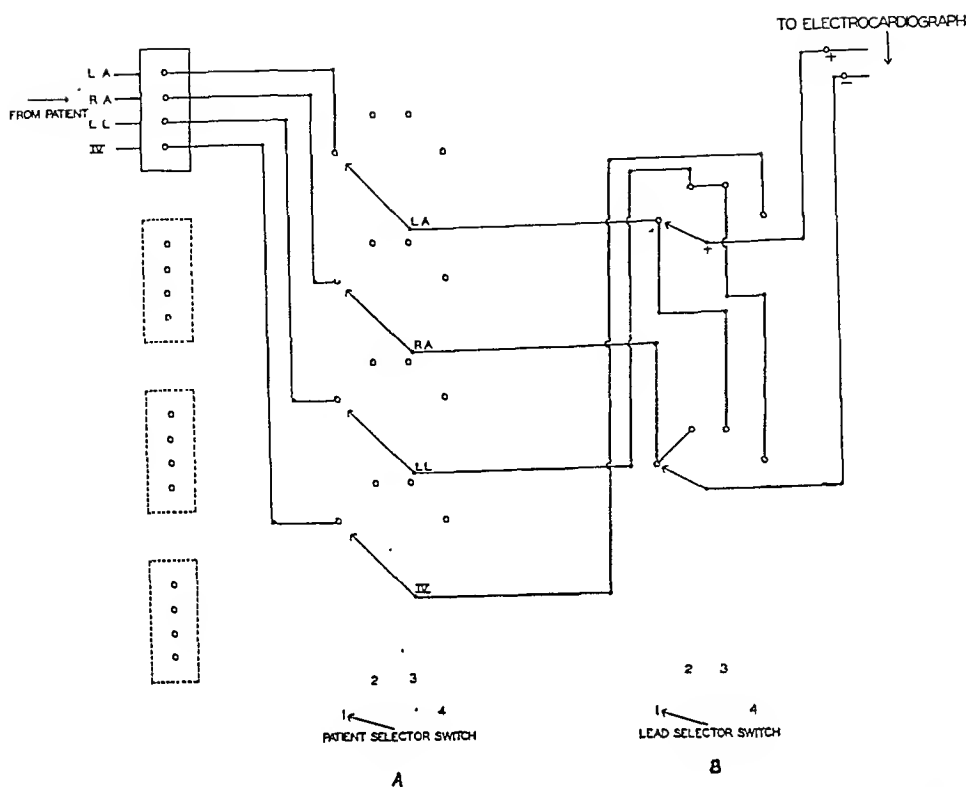


Fig. 2.—Wiring diagram of multiple patient-switch box. *LA*, to left arm; *RA*, to right arm; *LL*, to left leg; *IV*, to precordium.

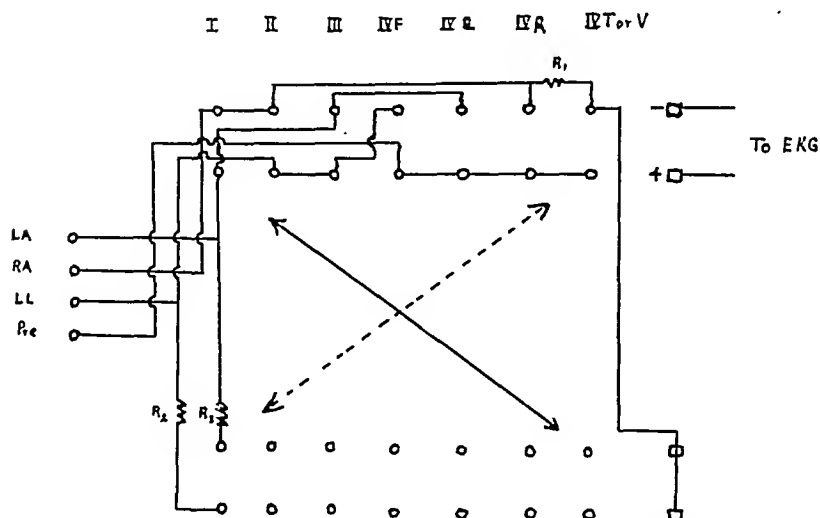


Fig. 3.—Precordial lead switch for one patient. Wiring diagram. Solid line of switch indicates position for obtaining Lead I. Broken line of switch indicates position for Lead IVT. Resistances shown ( $R_1$ ,  $R_2$ ,  $R_3$ ) are 5,000 ohms each. Intermediary positions of the switch will select any of the remaining leads indicated on the diagram without changing lead wires or position of electrodes.

first of these (*A*, Figs. 1 and 2) selects the patient whose record is to be taken at the moment. The second switch (*B*, Figs. 1 and 2) selects any one of the four leads which it is desired to record from that patient. On the right-hand end of the switch box there is a polarized jack into which is inserted a plug connected to two wires leading directly to the electrocardiograph. Any two lead wires of the electrocardiograph may be connected to the plug, with due regard to polarity. The corresponding lead is then selected by the lead switch on the control panel of the electrocardiograph.

The switches of the instrument are simple selector-switches, such as are used in the band switches of radio receivers. Inasmuch as thirty contact points can be obtained, with due regard to polarity, they can be adapted for any number of patients or leads desired.

The wiring diagram (Fig. 2) shows the arrangement for obtaining the three standard leads and Lead IVF. When used for one patient only, by simple additional connections, as shown in Fig. 3, the device can be arranged so that one-step movements of the switch will select the following precordial leads: IVF, IVR, IVL, or IVT. Lead IVT is obtained by adding the zero-potential electrode of Wilson to the circuit.

Because of the ease with which any special precordial lead may be obtained with this instrument, the argument that some one precordial lead should be used because it is easier to record than the others is no longer tenable.

## Department of Clinical Reports

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### VENTRICULAR TACHYCARDIA OF UNUSUALLY LONG DURATION (SEVENTY-SEVEN DAYS)

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VENTRICULAR tachycardia usually starts suddenly and terminates abruptly. The attacks last variable periods of time, usually minutes to hours, occasionally for days, and, on very rare occasions, a week or more. Long-continued attacks of ventricular tachycardia are rare, and are usually fatal. Wolferth and McMillan<sup>1</sup> reported four cases of paroxysmal ventricular tachycardia, and reviewed twenty-two cases from the literature, with electrocardiographic proof; the longest paroxysm persisted eleven days. Porter<sup>2</sup> reported an attack which lasted 153 hours, with recovery. Levine and Fulton<sup>3</sup> described an attack of fourteen days' duration which resulted in death. Salley<sup>4</sup> reported an attack which lasted eleven days and terminated in death. Elliott and Fenn<sup>5</sup> reported a ventricular tachycardia of thirty-two days' duration which resulted in death. Strong and Munroe<sup>6</sup> presented an unusual case of an attack which lasted twenty-three days, with recovery.

A patient who was admitted to the Methodist Hospital with ventricular tachycardia is of interest because of the unusually long duration of the attack; it lasted seventy-one days in the hospital, and probably began six days before admission, making a total of seventy-seven days.

#### CASE REPORT

A 59-year-old Polish cabinetmaker entered the hospital March 3, 1939, complaining of marked shortness of breath and a rapid heart; the symptoms began suddenly February 25, and were induced by excitement at a Union meeting. His doctor prescribed digitalis and bed rest. Several days later he complained of severe upper right abdominal pain, vomiting, and persistent hiccough. Six days after the onset he was brought to the hospital in an ambulance. Three years previously he had had a similar attack while walking a long distance and after a large meal, and remained in bed for two weeks. He continued his usual work until May, 1938, when he experienced another attack of rapid heart beating while dancing; this persisted for one month. From that time he complained of marked fatigue and dyspnea and palpitation while walking and working at his trade.

On admission he was very orthopneic, with an anxious expression, was moderately pale and cyanosed, and was hiccoughing continually and perspiring profusely. His

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weight was about 140 pounds; his temperature, 101.2° F. The eyes, nose, and throat showed no abnormalities. The external jugular veins were markedly distended, with questionable pulsations. Arterial pulsations were marked over each clavicle. The cervical lymph nodes and thyroid gland were not enlarged. The respiratory rate was 40 per minute. The apex beat was faintly palpable in the fifth intercostal space, halfway between the midclavicular and anterior axillary lines. The heart sounds were faint at the apex. The rate was 200, and the beating was regular. A fairly loud pericardial friction rub was heard in the fifth intercostal space at the parasternal line. No murmurs were audible. The blood pressure was 100/80. There was dullness at the bases of both lungs, with diminished breath sounds and crepitant râles, especially on the right side. The liver extended two fingerbreadths below the costal margin. There were marked distention and pulsations of the superficial arm veins, which remained distended when the arms were raised above the angle of Louis. The pulse volume was small. There was no edema of the legs or ankles.

Diagnosis on admission was enlarged heart, coronary artery thrombosis, auricular flutter, and congestive heart failure.

Digifoline (30 minims), morphine, Hoffmann's anodyne and carbogen were administered. An electrocardiogram showed ventricular tachycardia (Fig. 1). The patient was given quinidine sulfate in a dose of 3 grains every four hours; this was increased to 36 grains a day the following day. The erythrocyte count was 4,240,000, the hemoglobin, 13.6 Gm., and the leucocyte count, 22,900; 87 per cent of the leucocytes were polymorphonuclears. Chemical examination of the blood disclosed the following (in mg. per cent): nonprotein nitrogen, 40; sugar, 103; uric acid, 3.5; creatinine, 1.2; cholesterol, 174; chlorides, 410; calcium, 9.8; and phosphorus, 3.8. The CO<sub>2</sub> combining power was 44.3 volumes per cent. The blood Wassermann and Kahn reactions were negative. The sedimentation time was 20 minutes. Urinalysis was negative. Roentgenologic examination showed cardiac enlargement of the aortic and mitral type, with marked congestion of the bases of both lungs.

During the first 2.5 weeks the temperature averaged about 100° F., and gradually became normal during the third week; at the same time the leucocyte count gradually fell to 12,750 and the polymorphonuclears to 76 per cent, and the sedimentation time increased to two hours.

Nine grains of quinidine sulfate were given on the first day and 36 grains a day for the next five days. Daily electrocardiograms showed slowing of the ventricular rate to 140 on the seventh day; the duration of QRS remained at 0.16 sec. On the fifth day, 1/150 grain of atropine sulfate was administered with each dose of quinidine without change in rhythm. Quinidine was discontinued on the seventh day, and 0.5 gm. of quinine dihydrochloride was given intravenously. An electrocardiogram showed an increase in the ventricular rate to 158 and a QRS duration of 0.18 sec., but no change in the abnormal rhythm.

On the eighth day, 10 mg. of acetyl-beta-methylcholine chloride (mecholy) were administered subcutaneously, accompanied by carotid sinus pressure. An additional 10 mg. which were given three minutes later produced a slight reaction. The electrocardiogram showed an increase in the ventricular rate to 176, but no change in rhythm.

The following day 30 mg. of mecholy were given; this was followed by a fairly marked reaction, but no change in rhythm. The ventricular rate increased to 180. A few hours later signs of heart failure appeared, and 1.5 grains of digitalis were given orally every four hours during the next twenty-four hours; the electrocardiogram then showed an increase in the ventricular rate to 187, with a QRS of 0.16 sec.

On the eleventh day a second injection of 0.5 Gm. of quinine dihydrochloride was given, without reaction or change in rhythm. Quinidine sulfate in a dose of 36 grains a day was resumed, and, on the following day, the electrocardiogram

showed that the ventricular rate had diminished to 167, and there were fewer signs of heart failure. Since the heart rate diminished with quinidine therapy, the dose was increased to 72 grains a day, and three days later an electrocardiogram showed a ventricular rate 115 and a QRS duration of 0.22 sec. At this time the patient felt improved and had less pronounced signs of heart failure. Atropine sulfate in a dose of 1/50 grain was given subcutaneously on two occasions, together with 12 grains of quinidine, but no change in rhythm occurred.

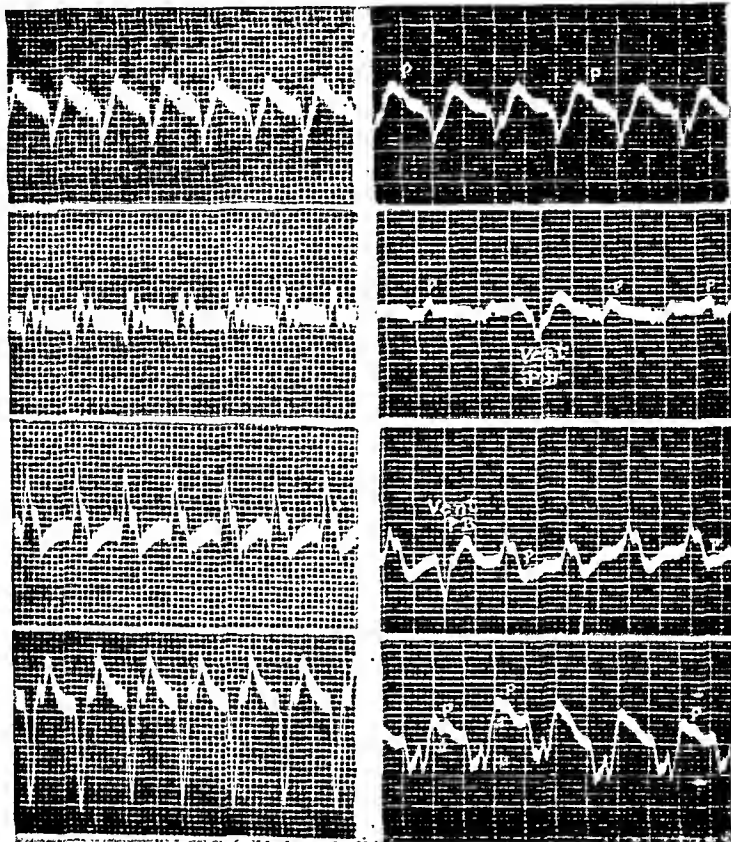


Fig. 1.

Fig. 2.

Fig. 1.—Ventricular tachycardia, rate 187, QRS 0.16 sec.

Fig. 2.—Ventricular tachycardia, rate 150; a ventricular premature beat is shown in Leads II and III. Questionable P waves in all leads.

On the sixteenth day the quinidine was reduced to 36 grains a day, and during the next three days the ventricular rate increased to 167.

During the night of the twentieth day, the patient was awakened by a choking feeling and rapid beating of his heart. No new abnormal physical signs were found. Morphine gradually relieved the attack. An electrocardiogram showed the same rhythm, with a ventricular rate of 167. The quinidine was increased to 54 grains a day, and, during the next three days, the ventricular rate diminished to 136, with a QRS duration of 0.20 sec.

During the fourth week the temperature remained normal and the patient was allowed a back rest. Quinidine in a dose of 54 grains a day was continued; the heart rate varied from 110 to 125, and the QRS duration, from 0.20 to 0.22 sec.

On the thirty-second day quinidine was discontinued, and 20 c.c. of a 10 per cent solution of magnesium sulfate were administered intravenously. Two minutes later the patient complained of a "burning feeling," perspired profusely, appeared pale,



became very apprehensive, and had a marked acceleration of respiration. Calcium chloride controlled the reaction. An electrocardiogram showed no change in rhythm and a ventricular rate of 130; QRS measured 0.20 sec. Quinidine sulfate in a dose of 60 grains a day was resumed, and the ventricular rate varied from 130 to 136 during the next six days.

On the thirty-eighth day a fluttering sensation around the heart became very annoying, and signs of pulmonary edema were found. Enlargement of the liver and edema of the ankles followed. The electrocardiogram showed ventricular tachycardia at a rate of 136, but with very low amplitude of the QRS deflections and T waves. Quinidine was discontinued. Digitalis (total dose 22.5 grains) was administered over a period of four days, with marked diminution of the pulmonary edema, congestion of the liver, and edema of the legs. The electrocardiogram showed an increase in the ventricular rate to 167, with persistence of the ventricular tachycardia. Quinidine in a dose of 36 grains a day was resumed, and the ventricular rate diminished to 150 after two days.

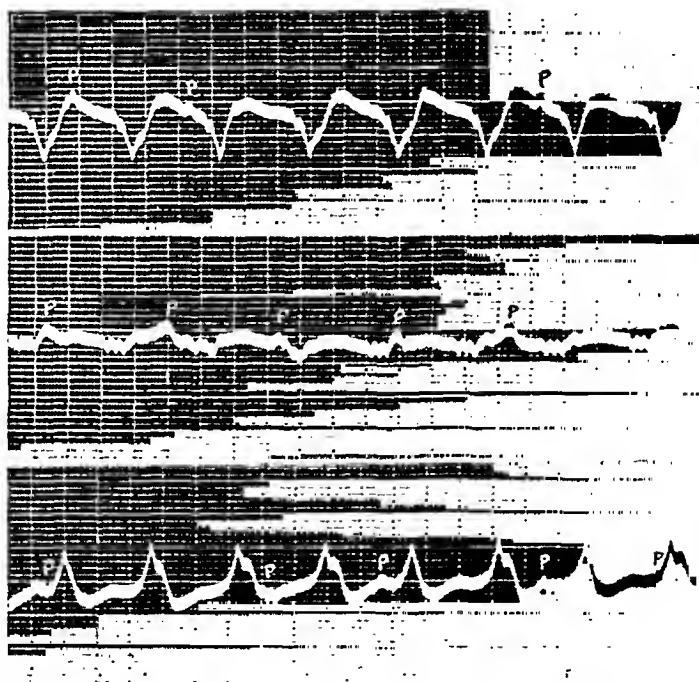


Fig. 3.—Immediately after an intravenous injection of 10 grains of quinidine. Ventricular tachycardia, rate 115, QRS 0.20 sec. P waves present in all leads.

On the forty-ninth day the quinidine was discontinued and mechohyl repeated. Thirty milligrams were injected subcutaneously, and twenty minutes later an additional 20 mg. were administered. A marked reaction followed, but no change in rhythm occurred. An electrocardiogram showed ventricular tachycardia, with a rate of 150.

On the fiftieth day 0.0005 Gm. of scillaren was administered intramuscularly, and one hour later the patient complained of a severe tight sensation across the anterior part of the chest. An electrocardiogram showed ventricular tachycardia, with a rate of 176. Thirty-six grains of quinidine and 120 grains of potassium bromide were given, and, on the following day, the electrocardiogram showed that the ventricular rate had been reduced to 136.

On the fifty-second day the patient developed an infarction in the lower lobe of the right lung. Morphine was required to relieve the pain and discomfort. The quinidine and potassium bromide were continued, and, in addition, a 50 per

cent solution of glucose was given intravenously twice a day. Daily electrocardiograms showed a gradual increase in the ventricular rate to 150, with occasional ventricular premature beats and questionable P waves (Fig. 2).

During the fifty-fourth day the patient became more apprehensive and restless, and had Cheynes-Stokes breathing. The apex beat was easily palpable in the sixth intercostal space at the anterior axillary line. The heart sounds were very faint and rapid. No murmurs were audible. The rhythm was occasionally irregular. Bilateral hydrothorax was present, and the liver was enlarged to the umbilicus. Marked edema extended up to the lower thighs. Mercurpurin intravenously had no effect. Coramine was given for several days with no beneficial results. The patient had been taking 36 grains of quinidine daily, and the ventricular rate varied from 120 to 136.

On the fifty-ninth day, 6 grains of quinidine sulfate were dissolved in 100 c.c. of physiologic saline solution and given intravenously over a period of twenty minutes. During the injection the respirations increased in depth and rate, and this was followed by nausea. Five hours later 10 grains more were injected, with occurrence of the same symptoms. An electrocardiogram made immediately after the injection showed ventricular tachycardia, a rate of 115, and a QRS duration of 0.20 sec. P waves were present at a slower rate (Fig. 3).

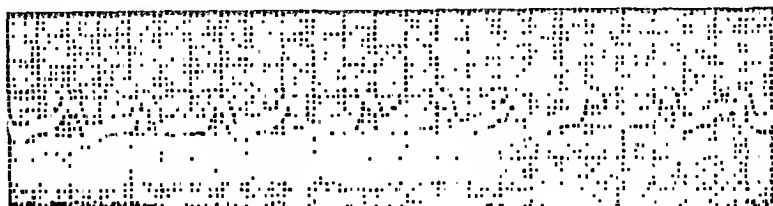


Fig. 4.—Lead III. After intravenous injection of 10 grains of quinidine. Ventricular tachycardia, rate 125, QRS 0.18 sec, P waves shown at the rate of 83 per minute.

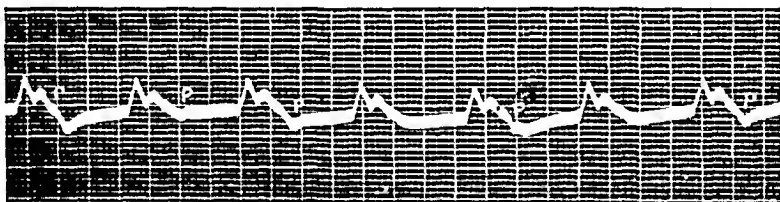


Fig. 5.—Lead III. After intravenous injection of 12 grains of quinidine. Ventricular tachycardia, rate 84, QRS 0.28 sec. P waves shown at slower and irregular intervals.

During the following week 36 grains of quinidine were given daily by mouth. The patient also received 120 grains of potassium bromide a day, 100 c.c. of a 50 per cent solution of glucose intravenously twice a day, and an occasional dose of morphine. The electrocardiograms showed continuous ventricular tachycardia, with occasional questionable P waves in the QRS groups and on the base line. The ventricular rate increased from 125 to 136.

On the morning of the sixty-ninth day, 10 grains of quinidine sulfate were dissolved in 100 c.c. of sterile distilled water and given intravenously by the drop method, over a period of fifty minutes. An electrocardiogram after the injection showed no change in rhythm, but an increase in the rate to 125. P waves were present with a slower (rate 83), regular rhythm (Fig. 4).

Four hours later another intravenous injection of 12 grains of quinidine sulfate was almost completed by the same method when the patient suddenly became unconscious and pulseless. The electrocardiogram at this time showed ventricular

tachycardia, with a rate of 84; the duration of QRS was approximately 0.28 sec. P waves were noted at a slower rate and at irregular intervals (Fig. 5).

Seven minims of adrenalin were injected subcutaneously, but the patient did not regain consciousness until thirty minutes later. One minute after the injection of adrenalin the ventricular rate increased to 100, and, in two minutes, the rate increased to 125, where it remained until he regained consciousness. Electrocardiograms made during this time continued to show ventricular tachycardia. During the next twenty-four hours the patient became steadily worse. An electrocardiogram showed ventricular tachycardia, with a rate of 136 and a QRS of 0.16 sec. The heart sounds became very faint, with signs of heart failure. Pulmonary edema occurred early the next morning, and the patient expired.



Fig. 6.—Marked enlargement of the heart, showing the dilated and thin left ventricular wall at the apex region. The large, lighter area, involving more than half of the wall and interventricular septum, shows the extent of the dense fibrosed infarct resulting from thrombosis 1 cm. from the opening of the left coronary artery. The orifices of both coronary arteries are patent.

*Post-Mortem Examination.*—The heart weighed 540 Gm. (Fig. 6). The epicardium was transparent and glistening. The apex was enlarged and rounded, with a very thin wall. The left ventricular cavity was 10 cm. long, and was filled with old and new blood clots. The upper ventricular wall was firm, and measured 1.2 cm. At the apex the wall measured 3 mm., and consisted of epicardium, endocardium, and a thin layer of fibrous tissue. A section cut 1 cm. below the aortic valve showed streaks of fibrous tissue extending throughout the entire width of the septum. The papillary muscles appeared normal. The right auricle was markedly dilated. The valve orifices were of normal diameter, and the valves showed no lesions. The mouth of the left coronary artery was patent, and the first centimeter of the vessel was normal. The next centimeter was markedly thickened and calcified, and calcified plaques occluded the lumen. The right coronary artery was patent and had a thin and pliable wall. The aorta measured 7 cm. in the circumference, and showed a few small yellowish areas.

The right pleural cavity contained 1,500 c.c. of clear yellow fluid. The right upper lobe showed diffuse consolidation. The right lower lobe contained an infarct 5 cm. in diameter, and a smaller infarct, 3 cm. in diameter, was found in the left lower lobe. The pulmonary vessels and hilar nodes were normal.

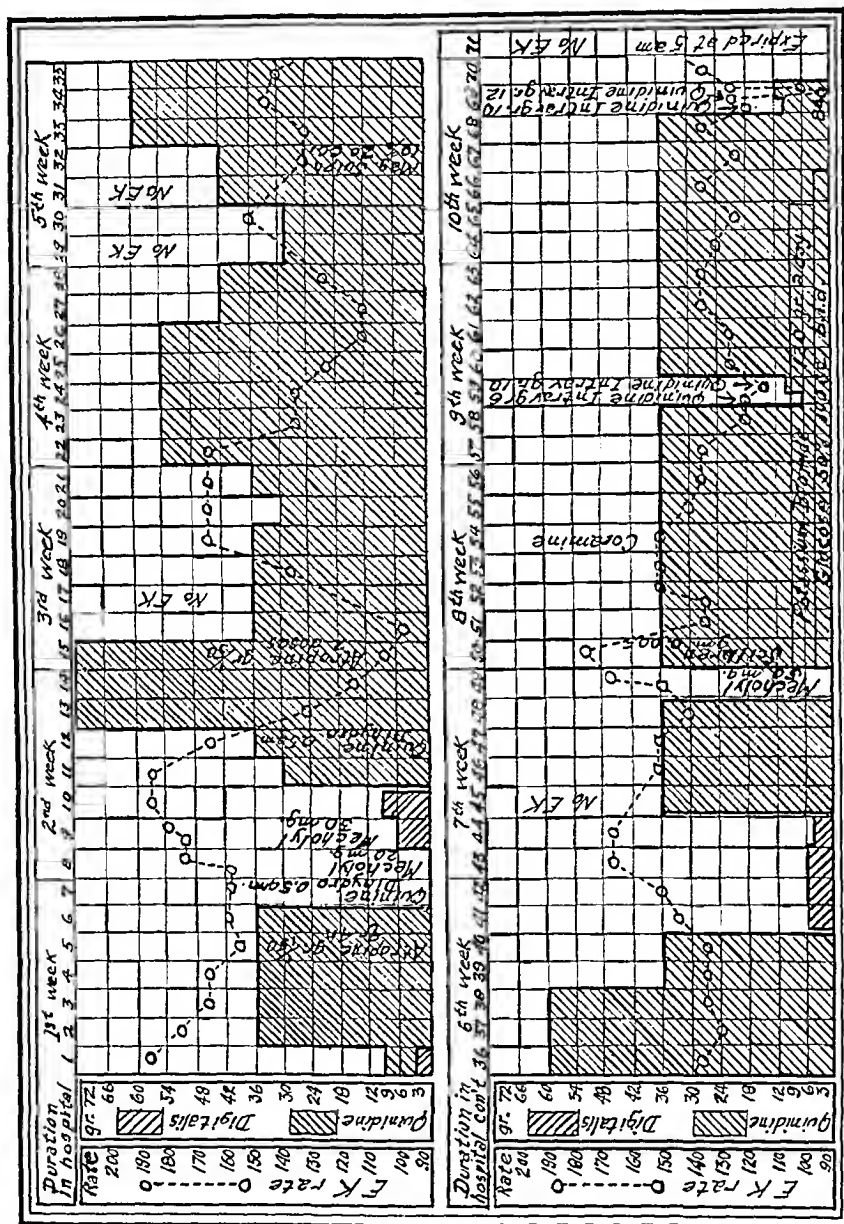


Fig. 7.—The effect of drugs during treatment in hospital. Ventricular tachycardia of unusually long duration.

The liver weighed 1,540 Gm. The gall bladder, spleen, pancreas, and adrenals were normal. An infarct 5 cm. in diameter was found in the right kidney.

Microscopic examination of a section from the apex showed that practically all of the myocardium had been replaced by dense, almost acellular, fibrous tissue. Numerous large and small areas of fibrosis were found throughout the entire myocardium. A section of the septum showed areas of fibrous tissue. A cross section of the left coronary artery showed marked sclerotic thickening of the intima, with occlusion of the lumen.

## DISCUSSION

Ventricular tachycardia is a serious cardiac disorder, and attacks of long duration are usually fatal. It has been suggested by Levine and Fulton that circus movement in the ventricle is the cause of ventricular tachycardia, and that this accounts for the slight irregularity of the ventricular complexes. Many cases of paroxysmal ventricular tachycardia during and following the administration of digitalis have been reported. Before admission to the hospital this patient received digitalis (exact amount not known), and, after admission, received 3 grains of digitalis before the first electrocardiogram was made. All forms of therapy failed to restore normal rhythm. Because of the increasing signs of heart failure, 22.5 grains of digitalis were administered; this was followed by lessening of the congestion, but the heart rate increased. Atropine in combination with quinidine did not alter the rhythm. Several injections of acetyl-beta-methylcholine chloride, with carotid sinus pressure, had no effect on the rhythm. Magnesium sulfate intravenously caused an alarming reaction which subsided after an injection of calcium; there was no effect on the rhythm. Two intravenous injections of quinidine dihydrochloride were given without reaction or change in rhythm, but they were followed by an increase in the heart rate. Large doses of quinidine sulfate made the patient more comfortable and could be relied upon to slow the ventricular rate until a few days before death, but never changed the rhythm. On the fifty-ninth day an intravenous injection of 6 grains of quinidine sulfate, followed by another of 10 grains, did not cause a marked reaction or change in rhythm, but another attempt to give quinidine intravenously caused a sudden and alarming reaction. The patient was revived with adrenalin. No further attempt was made to give medication intravenously because of the seriousness of the patient's condition.

## SUMMARY

This is the report of a case of coronary artery thrombosis, with infarction and involvement of the interventricular septum, marked enlargement of the heart, and dilatation of the left ventricular wall, complicated by ventricular tachycardia of seventy-one days' (known) duration.

Because of the sudden onset of a rapid heart rate, with marked dyspnea, immediately after undue excitement six days before entering the hospital, it is reasonable to assume that the ventricular tachycardia was continuous for seventy-seven days. The classical anginal syndrome was not conspicuous at the onset, but the presence of marked dyspnea, palpitation, and certain clinical signs led to the diagnosis of coronary artery thrombosis, with severe myocardial damage. The ventricular tachycardia was demonstrated by numerous, almost daily, electrocardiograms. Digitalis was given on two occasions in an attempt to control

the heart failure. The ability of large doses of quinidine sulfate to slow the ventricular rate was demonstrated. No form of treatment abolished this abnormal rhythm. The clinical, electrocardiographic, therapeutic, and post-mortem observations are reported.

I wish to express my indebtedness and appreciation to Dr. Harold E. B. Pardee for his helpful electrocardiographic interpretations, suggestions concerning treatment, and aid in preparation of this report.

#### REFERENCES

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Sabathie, L. G., and Pianetto, M. B.: The Coronary Arteries of the Horse. *Rev. argent. de cardiol.* 8: 184, 1941.

In the horse, as in most herbivorous animals, the right coronary artery is much larger than the left. The sinus node has a double blood supply (from the left circumflex and the right coronary arteries). The Aschoff-Tawara node receives its blood supply from the posterior and superior septal arteries, branches of the posterior descending artery which also irrigates the His bundle. The bundle branches are irrigated by the anterior and posterior septal arteries.

The left coronary artery supplies the anterior half of the left ventricle, a region 4 cm. wide of the right ventricle adjacent to the anterior interventricular groove, all the left auricle but its posterior wall, a zone of the right auricle anterior to the orifice of the superior vena cava, and the anterior half of the interventricular septum.

The right coronary artery irrigates the right ventricle excepting the zone adjoining the anterior interventricular groove, the posterior half of the left ventricle, the right auricle excepting the zone anterior to the superior vena cava, the posterior wall of the left auricle, and the posterior half of the interventricular septum.

Both coronary arteries are connected by anastomosis.

AUTHORS.

Perlow, S., Killian, S. T., Katz, L. N., and Asher, R.: Shock Following Venous Occlusion of a Leg. *Am. J. Physiol.* 134: 755, 1941.

In the course of experiments in which attempts were made to produce chronic edema the procedure of ligation of the iliac vein with injection of various materials distally into the vein was initiated. In a number of instances marked edema of the legs developed and the animals died within twenty-four hours, sometimes within four to six hours. The possibility of shock as the cause of death suggested itself, and this was investigated in a series of eight dogs.

Nearly complete venous occlusion of a hindlimb of the dog leads to shock which terminates fatally. This procedure offers a simple way of studying the course of shock and the utility of some of the proposed therapeutic agents to counteract shock.

The mechanism appears to be the marked loss of fluid into the leg, at first plasma and later whole blood, which amounts to from 4 to 6 per cent of the body weight. This loss is brought about first by an increase in the capillary hydrostatic pressure of the occluded limb soon aggravated by loss of capillary permeability. These experiments tend to support the view that the primary mechanism in shock is the local loss of fluid from the blood.

AUTHORS.

Wiggers, C. J.: Cardiac Adaptations in Acute Progressive Anoxia. *Ann. Int. Med.* 14: 1237, 1941.

In acute progressive anoxia the supply of oxygen to cells is not conditioned solely by the degree of pulmonary ventilation and the oxygen-carrying capacity of the blood; it involves also an increased blood flow.

The circulatory reactions characteristic for man, breathing gas mixtures with decreasing oxygen volumes (20>6 per cent) can be duplicated in lightly anesthetized dogs. Such experiments have the advantage that the mechanisms by which cardiac adaptations operate to increase blood flow can be analyzed more thoroughly than in man.

During hypoxia, corresponding to progressive decrease in respired oxygen volumes to about 12 per cent, to blood oxygen saturations above 75 per cent or altitudes of 15,000 feet, blood flow is increased (a) regionally by reciprocal constriction and dilatation of vessels causing redistribution of blood flow and (b) generally by acceleration of the heart. The latter is due to decreased vagal tone, increased accelerator nerve activity, and perhaps some direct effect on the S-A node. Stroke volume is not affected otherwise than during any cardiac acceleration. The vigor of ventricular contractions increases, and the period of systolic expulsion shortens. Vasomotor changes probably occur, but there is no dynamic evidence that they are reflected in the changing systolic and diastolic pressures. Effective venous pressures fall slightly, not through reduced venous return but due to greater minute output by the faster heart.

During true anoxia, which begins when oxygen of the inspired air is progressively decreased below 12 per cent, the heart responds with greater stroke volumes and with further increase in velocity of ejection. The economy of effort is enhanced. Experiments on dogs with "controlled circulation," i.e., in animals whose heart rate, arterial diastolic and venous pressures, as well as alveolar carbon dioxide are kept constant, have demonstrated that the increased systolic discharge is accompanied by increase in diastolic size, independently of changes in venous pressure. Such compensatory reactions probably could not occur without the unquestioned dilatation of coronary vessels.

Further decline of oxygen in the inspired air to 7 or 6 per cent, corresponding to arterial oxygen saturations between 50 and 35 per cent and to altitudes up to 30,000 ft., leads to a circulatory crisis. Arterial pressures decline abruptly; pulse pressure is reduced; systolic discharge decreases; venous pressure rises tremendously; and various types of conduction and rhythm disturbances may occur. No evidence exists that peripheral vasomotor failure is concerned. The circulatory crisis is essentially an acute congestive heart failure due to the depressant effect of anoxia on the myocardium. It probably supervenes when the increasing coronary flow can no longer keep pace with the rapidly diminishing tension of oxygen in the blood.

AUTHOR.

Dressler, W.: Studies in Physical Diagnosis of the Heart. I. Percussion. *Brooklyn Hosp. J.* 3: 196, 1941.

Percussion is a useful source of clinical information, provided that the method is simplified and subjective error reduced. Attempts to determine the position of the cardiac borders are futile and should be abandoned. This applies also to the distinction of absolute and relative dullness. Only marked dullness closely approaching flatness should be evaluated in the diagnosis of cardiac enlargement.

Certain abnormal areas of marked dullness signify enlargement of distinct portions of the heart. The normal area of marked dullness in adults extends from the left margin of the sternum to about 0.5 cm. inside the left midclavicular line,



and upward to the fourth rib. Craniad expansion of this dullness into the third left interspace characterizes dilatation of the pulmonary conus. Expansion of the cardiac dullness toward the lower half of the sternum signifies dilatation of the inflow tract of the right ventricle. Marked dullness to the right of the sternum in the fourth and fifth interspaces indicates dilatation of the right auricle.

Percussion of the sternum is particularly useful inasmuch as it may yield information about enlargement of the right ventricle earlier and more distinctly than it is shown by radiologic examination. Marked and extensive dullness over the sternum is also an important sign of pericardial effusion. As far as enlargement of the left ventricle is concerned percussion yields less reliable results than palpation of the apex beat and roentgen-ray study.

AUTHOR.

Huber, J. F.: The Arterial Network Supplying the Dorsum of the Foot. *Anat. Rec.* 80: 373, 1941.

The "textbook picture" of the arterial supply of the dorsum of the foot in man was present in only 5.5 per cent of the 200 feet dissected.

An arterial network having an almost constant pattern was demonstrated in the dorsum of the foot which can serve as a basis for a practically universally applicable description of the arterial supply of this region when information is added as to how frequently each part of that network may be of significant size, such information having been given in the description of the individual vessels making up the network.

The anterior medial and anterior lateral malleolar arteries were found to branch more commonly from the dorsalis pedis artery rather than from the anterior tibial artery, as usually stated.

No one vessel was found which seemed to merit being called "the anterior perforating artery," but in its place five vessels are described for which the name "anterior communicating arteries" is suggested.

A branch of the anterior tibial artery about 5 cm. above the ankle joint, a previous description of which has not been found, was present as a vessel of significant size in about half of the feet, either contributing to, or being the principal source of, the perforating branch of the peroneal artery.

A comparison of the findings for negro and white cadavers seems to indicate that the negro more closely approximates the "textbook picture" as far as the blood supply of the dorsum of the foot is concerned.

Although little exact and detailed bilateral symmetry was found, there was a rather high degree of bilateral similarity.

AUTHOR.

Rutherford, R. B., Godfrey, E. W., and Griffith, J. Q., Jr.: Roentgenographic Observations Suggesting Difference Between Total and Circulating Blood Volume. *Am. J. Physiol.* 134: 808, 1941.

After a strong vasoconstricting agent, pitressin, blood volume measured by a dye method is greatly reduced. We suggest that a considerable amount of blood may be trapped in areas of the peripheral circulation so that actively circulating blood volume may be much less than total blood volume. The blood still circulating shows relatively slight changes in hematocrit red cell volume or in plasma protein concentration. The presence of blood vessels in the extremities containing blood but without active circulation is shown by the following: (1) By microscopy, the skin capillaries contain red cells, but there is no flow. (2) Thorotrast introduced into the general circulation before the administration of pitressin remains in and outlines

the vessels of the extremities. (3) Blood cannot be secured by cutting a tail vein. (4) Thorotrast introduced into the general circulation after the injection of pitressin either does not enter into and outline the vessels of the extremities or does so tardily and to a lesser extent.

AUTHORS.

Cossio, P., Sabathie, L. G., and Berconsky, I.: Alterations of the S-T Segment and of the T Wave During or After Prolonged Crises of Paroxysmal Tachycardia. *Rev. argent. de cardiol.* 8: 168, 1941.

In four relatively young patients during or after prolonged and repeated crises of paroxysmal tachycardia of supraventricular or ventricular origin, an opponent depression of the S-T segment and a negative T wave in Leads II and III (three cases) or in Leads I and II (one case) were observed. Autopsy of one case showed cardiac dilatation, integrity of the coronary vascular system, and absence of focal necrobiosis.

The electrocardiographic alterations described are thought to be due to the enlargement of the heart or to right ventricular strain. But whatever their cause it is a fact that they cannot always be imputed to a real coronary insufficiency. Five other observations have been found in the literature, one of them with necropsy, confirming this conclusion.

AUTHORS.

Bohning, A., Katz, L. N., Langendorf, R., and Blumenthal, B.: Intraventricular Block, Including So-Called Bundle Branch Block. *Am. J. M. Sc.* 202: 671, 1941.

An analysis was made of the electrocardiograms of 176 persons with intraventricular block. They were classified according to the differences in pattern found in the limb and chest leads. The types were related to the probable delay in stimulation of the right and left ventricles, as suggested by the averages of the Q-E intervals (the time from the onset of QRS to the rise of the subclavian arterial pulse) in each group. Further, an analysis of some detail was made of the findings in twenty-five autopsied cases.

AUTHORS.

Prinzmetal, M.: Calculation of the Venous-Arterial Shunt in Congenital Heart Disease. *J. Clin. Investigation* 20: 705, 1941.

A simple method has been described for determining the presence of a venous-arterial shunt in congenital heart disease, the magnitude of the shunt, and the true pulmonary circulation time in the presence of shunt.

AUTHOR.

Levine, H. B., and White, P. D.: What Sensible Living and Natural Recovery Can Do for a Cardiac Patient. *New England J. Med.* 225: 101, 1941.

Seven patients with severe heart disease appeared to have unfavorable prognoses at the onset of their illness but through natural recovery or sensible living were able to lead long and useful lives. This emphasizes the statement that in acute heart disease "functional recovery may be so complete that the ultimate prognosis is good for many years after." It is not to be inferred, however, that one may dispense with medical attention. Furthermore, every person should seek medical counsel at the onset of symptoms, whether or not they are of cardiac origin.

AUTHORS.

**Ernstene, A. C., and Schneider, R. W.: Angina Pectoris in Young Individuals With Aortic Insufficiency. Am. J. M. Sc. 202: 737, 1941.**

Six cases of angina pectoris of decubitus in young persons who had rheumatic heart disease with pronounced aortic insufficiency have been reported. All of the patients experienced repeated nocturnal attacks, and it was of these seizures that they principally complained. In four of the six patients, attacks also were induced by exertion. Prominent vasomotor changes, such as flushing of the face, sweating, palpitation and throbbing of the vessels of the neck, accompanied the pain in five patients. The pain in each case was similar in location, quality, and radiation to that of the common form of angina pectoris and usually was relieved promptly by amyl nitrite or nitroglycerin. In none of the cases was the initial occurrence of angina pectoris precipitated by active rheumatic infection.

The average duration of life after the first attack of angina pectoris due to aortic regurgitation is greater than in patients who have angina pectoris due to coronary artery disease, but the prognosis is uncertain in the individual case because of a distinct liability to sudden death.

There is no medical measure that is effective in preventing the occurrence of the attacks in this form of angina pectoris. Various surgical measures have been employed and often with considerable benefit. Because of limited experience, however, no statement can be made as to the relative value of the different procedures.

The earlier literature concerning this form of angina pectoris has been reviewed briefly, and the pathogenesis of the attacks has been discussed.

AUTHORS.

**Southworth, H.: Subacute Staphylococcus Endocarditis and Staphylococcus Bacteremia Without Endocarditis With a Report of the Favorable Effect of Sulfanilamide and Sulfathiazole in Two Cases. Ann. Int. Med. 14: 1180, 1941.**

Two cases are reported of prolonged (over five months) staphylococcus bacteremia without an obvious focus of infection other than possibly an endocarditis. Six similar instances have been gathered from the literature.

In one case staphylococci were consistently present in the blood stream for seventeen months, and yet the patient maintained relatively good health.

In both cases the staphylococcus was antigenically a group C organism.

The difficulty of determining without autopsy whether or not there really is an endocarditis is stressed.

The favorable influence in one case of sulfanilamide and in another of sulfathiazole is described.

AUTHOR.

**Geckeler, G. D.: Phonograph Records of Heart Sounds, Murmurs and Arrhythmias. Am. J. M. Sc. 202: 685, 1941.**

These records do well for self-teaching as well as for class work. The person listens with his stethoscope as the record is being played, simply holding the chest piece in his hand, with the bell or diaphragm exposed to the air. It is suggested that he sit comfortably in a quiet room and close his eyes (it always helps to blot out as many sensory stimuli as possible).

It is hoped that these records will fill the need of the family physician who has been away from a center for a number of years and who needs a "refresher." They are of value in undergraduate and post-graduate teaching, and they may have value to draft board examiners. Because of their inclusion of even rare auscultatory abnormalities, they are of use for reference.

AUTHOR.

**Cahan, J. M.: Rheumatic Heart Disease in Families.** Pennsylvania M. J. 44: 481, 1941.

This report is based on a study made by reviewing 1,627 private cardiac records of 1,517 children and 110 parents. These records showed that 629 patients had rheumatic heart disease at the time of examination or re-examination, some time between the years 1920 and 1940. In eleven of these the acquired lesion was combined with a congenital acyanotic heart condition. Families in which a parent and a child, or two siblings, were afflicted with rheumatic heart disease were selected for further study. A complete history relating to rheumatic symptoms was obtained of the entire family, and a careful examination was made of every available member of the family. So far, fifty-three families have been studied. The number of children in each of these families varied from one to ten and totaled 174, eighty-four boys and ninety girls. Two of the families had one child each; twenty-three families, two children each; ten families, three each; eight families, four each; two families, five each; five families, six each; two families, seven each; and one family, ten children. At the time of examination 128 of these children had rheumatic heart disease. Rheumatic heart lesions were also found in one of the eighteen grandchildren, in thirty-seven of the fifty-five parents examined, and in five of the seven grandparents examined. Altogether, 171 rheumatic heart cases were found among the 235 persons examined.

AUTHOR.

**Ash, R.: The Evolution of Rheumatic Heart Disease in Childhood.** Pennsylvania M. J. 44: 484, 1941.

The changes in physical signs of the heart that occurred in a group of 549 rheumatic children over an average period of nine years have been described. The majority of children destined to develop rheumatic heart disease had already done so in their initial illness. Moreover, the early months of the disease were relatively the most fatal. Methods designed to influence rheumatic infection must therefore be instituted upon the earliest appearance of any manifestation.

Recurrences were the predominant factor in the maintenance and in the fresh appearance of cardiac damage. In a small percentage of cases, however, signs of valvular disease made their appearance in the seeming absence of infection after a latent period of years.

Because of the cyclic nature of the disease, the tendency to recurrences, and the possibility of insidious development of valvular lesions, rheumatic patients should be kept under continuous medical supervision, with careful periodic examinations for signs of infection as well as signs of cardiac damage.

AUTHOR.

**Berk, L. H.: Cardiovascular Syphilis.** New York State J. Med. 41: 223, 1941.

Difficulties in diagnosing cardiovascular syphilis are outlined briefly, and the importance of the involvement of the coronary ostia in prognosis is stressed.

Analysis is made of 172 cases. Included are twenty early and 117 advanced cases, thirty-five with necropsy. These comprise thirty-nine cases of uncomplicated aortitis, twenty-three cases of aneurysm, and 124 cases of aortic insufficiency.

An abnormal electrocardiogram with progressive serial changes is found to be (in the absence of acute myocardial infarction) strongly suggestive of syphilitic aortitis with probable coronary ostial stenosis.

It is demonstrated that a normal or borderline electrocardiogram in a syphilitic patient under 45 years of age may become positive after the exercise test is given, thus establishing the diagnosis of aortitis with probable coronary ostial stenosis.

The importance of the electrocardiographic study made with the exercise test is emphasized as the only safe means of establishing the diagnosis of latent coronary ostial stenosis.

Routine use of the electrocardiographic study and exercise test in early cases with a systematic follow-up in subsequent years is urged in order to discover cardiovascular syphilis at an earlier stage than has been possible heretofore.

AUTHOR.

Weinstein, J.: **Public Health Aspects of Cardiovascular Syphilis in New York City.** *New York State J. Med.* 41: 234, 1941.

An analysis of the available morbidity and mortality statistics and a consideration of the economic aspects of cardiovascular syphilis in New York City show that this disease is an important public health problem.

From a practical public health point of view no conspicuous change has taken place in New York City in the reported deaths from aortic aneurysm during the past decade and a half. Apparently, syphilis in a number of persons has not been recognized early enough or properly treated in the past to avoid later complications in the circulatory system.

The outlook for cardiovascular syphilis in the future is full of promise, and treatment of syphilis in its earliest possible stage is continued intensively for an adequate period of time.

Past experience has taught us that aortic syphilis will develop in a certain number of persons despite energetic and prolonged treatment of early syphilis. In this respect more knowledge is wanted, and further efforts in the direction of research on syphilis treatment and its evaluation are indicated.

AUTHOR.

Ritchie, G.: **Metastatic Tumors of the Myocardium.** *Am. J. Path.* 17: 483, 1941.

Sixteen cases of metastatic tumors of the myocardium are reported, with a tabulation of certain features and a brief discussion. Thirteen different types of primary tumors were represented, and there was considerable variation as to route of metastasis and mode of growth within the muscle. In no case had a clinical diagnosis of cardiac invasion been made.

AUTHOR.

Wakerlin, G. E., and Johnson, C. A.: **The Effect of Renin on Experimental Renal Hypertension in the Dog.** *J. A. M. A.* 117: 416, 1941.

Daily intramuscular injections of hog renin for four months produced striking reductions in the blood pressures of dogs with renal hypertension, whereas heat-inactivated hog renin and active dog renin were without effect.

No detected toxic manifestations resulted from the injections of renin or from the reductions in blood pressures. The sera of the dogs treated with hog renin, but not the sera of the dogs given injections of inactivated hog renin or dog renin, neutralized the acute pressor effect of renin (antirenin).

Daily intramuscular injections of hog renin into two normotensive dogs before and after constriction of the renal arteries prevented the development of hypertension. The mechanism of these therapeutic and prophylactic effects of hog renin in experimental renal hypertension in the dog is not clear. Most probably an immune (anti-hormone?) response to heterologous hog renin is involved.

AUTHORS.

**Grimson, Keith S.:** The Sympathetic Nervous System in Neurogenic and Renal Hypertension. *Arch. Surg.* 43: 284, 1941.

The author and co-workers have demonstrated previously that total sympathectomy prevents the pressor response to increased intracranial pressure. The experiments in this investigation have shown that total sympathectomy also prevents or abolishes for a time the elevation of blood pressure that follows section of the modulator nerves. Various types of localized sympathetic denervation have not prevented either of these types of neurogenic hypertension. It therefore seems likely that better results may be expected from total sympathectomy than from partial sympathectomy directed toward localized vascular beds, such as the splanchnic area.

NAIDE.

**Corcoran, A. C., and Page, I. H.:** Renal Blood Flow and Sympathectomy in Hypertension. *Arch. Surg.* 42: 1072, 1941.

Observations of preoperative and postoperative renal blood flow and filtration fractions in two cases of essential hypertension treated by extensive sympathectomy are reported. The operation did not increase renal blood flow or decrease the degree of efferent arteriolar constriction in either case. These observations are in accord with experimental data obtained from chronic experiments in animals and with other observations on the effect of renal denervation and sympathectomy in man.

It is concluded that the benefits of sympathectomy in cases of hypertension do not depend on improvement of renal circulation resulting from interruption of renal nerves. The suggestion is made that the decrease of arterial pressure which follows sympathectomy in hypertensive man is an expression of denervation of the reactive visceral splanchnic innervation, with resultant partial failure of venous return, most evident in the erect position. The decrease of venous return limits cardiac output and thus tends to decrease arterial pressure. It is further suggested that the decrease of arterial pressure is in itself an adequate explanation of the clinical improvement which may follow such an operation, since it may prevent the further spread of arteriolar lesions.

The probable relation of the renal vasopressor system to hypertension is reviewed, and it is noted that renal vasoconstriction in cases of hypertension is probably humoral rather than neurogenic in origin. The view is proposed that decreased arterial pressure occurring as a result of sympathectomy may arrest the progress of renal arteriolosclerosis in a hypertensive patient and that, since these arteriolar lesions may contribute to the release of renin and the activity of the renal vasopressor system, sympathectomy may thus interrupt for a time the progress of the disease.

AUTHORS.

**Abeshouse, B. S.:** Hypertension and Unilateral Renal Disease. *Surgery* 10: 147, 1941.

This is a review of the literature on hypertension and unilateral renal disease with a report of sixteen cases. In this group of patients, notwithstanding the fact that a definite causal relation between the hypertension and the unilateral renal disease could be established, neither an immediate nor a late reduction in arterial pressure occurred after nephrectomy. This may be explained on the basis that either the unilateral diseased kidney was not the sole etiological factor or the disease process had been present over a long period of time and had caused secondary arterial changes in its mate or elsewhere in the body which were responsible for the persistent hypertension.

It is important that an adequate period of time (at least one year) should elapse following operation before one attempts to evaluate the permanency and extent of the reduction in arterial blood pressure. In view of the uncertain end results and insufficient period of observation in the reported cases, there appears to be no justification for considering nephrectomy as a panacea for the cure of hypertension in every case of chronic unilateral disease of the kidney.

Every case of hypertension associated with unilateral renal disease should be subjected to a careful and complete urologic study in order to select those cases suitable for operation and to avoid the needless sacrifice of renal tissue in those patients who can ill afford to lose it.

It must be remembered that nephrectomy may be fatal in cases of hypertension of long duration or those whose clinical course is suggestive of the so-called "malignant hypertension."

NAIDE.

**Brill, I. C., and Meissner, W. A.: The Role of Coronary Artery Disease in the Etiology of Auricular Fibrillation. *Ann. Int. Med.* 14: 1341, 1941.**

Data obtained from an examination of the records of 400 autopsied cases tend to suggest the following conclusions.

In the absence of congestive heart failure or acute coronary occlusion, coronary artery disease is not a cause of auricular fibrillation.

Congestive heart failure involving the left side of the heart, regardless of the underlying pathologic lesion, tends to favor the development of auricular fibrillation. It is suggested that stretching of the left auricle might be an important factor in this process.\*

Coronary artery disease, although not a direct cause of auricular fibrillation, nevertheless may be concerned indirectly in the genesis of the arrhythmia by first inducing congestive failure. This mechanism is offered as a probable explanation for the frequent appearance of transient auricular fibrillation following an attack of acute coronary thrombosis, although this arrhythmia occurs very rarely in angina pectoris of coronary origin prior to the onset of congestive failure.

In a case already in congestive failure, the subsequent appearance of auricular fibrillation affords no additional information which might serve as an aid in determining the presence or the absence of coronary artery disease.

An analysis of the records of 100 cases of angina pectoris under active treatment confirms the observation already noted by many authors that auricular fibrillation is rare in angina pectoris of coronary origin, except in the presence of congestive failure.

AUTHORS.

**Nelson, M. G.: Intimal Coronary Artery Haemorrhage as a Factor in the Causation of Coronary Occlusion. *J. Path. & Bact.* 53: 105, 1941.**

Changes in the vessel wall are considered to be of greater importance in the development of coronary occlusion than changes in the blood.

The most common predisposing disease is coronary atherosclerosis.

Many sinusoidal blood vessels are found in relation to intimal atheromatous plaques. These vessels occur in two situations, either deep in the intimal tissues close

\*The effect of failure of the left ventricle upon the left auricle is often indicated by changes in the electrocardiogram relating to auricular activity, which are strikingly similar to those occurring in mitral stenosis. These changes which are believed to be due to hypertrophy and dilatation of the left auricle consist of a widened P wave of low voltage, usually bifid or flat-topped. They have been described recently by Wood and Selzer as a new and early sign of left ventricular failure.

to the media, or more superficially, near the endothelium. In the majority of cases they are surrounded by chronic inflammatory changes.

Hemorrhage from these sinusoids is a not uncommon finding in coronary atherosclerosis. Hemorrhages into the deeper zones of the intima heal by granulation tissue in which new capillaries are numerous. Such a process increases the fibrosis and the vascularity of the intima and predisposes it to further hemorrhage.

Superficial intimal hemorrhage is a most important factor in the etiology of coronary occlusion. It was present in eleven of seventeen patients examined, but, in nine of these, thrombotic occlusion of the lumen was also present.

The factors determining the intimal hemorrhage are probably weakening of the sinusoidal wall by toxic action and transient raised intraluminal pressure induced by exertion or emotion. In such cases superimposed intravascular thrombosis may be delayed until a subsequent period of bodily or mental rest.

AUTHOR.

Boyer, N. H., Leach, C. E., and White, P. D.: *The Immediate Prognosis of Congestive Heart Failure.* *Ann. Int. Med.* 14: 2210, 1941.

The immediate prognosis in 748 patients with congestive heart failure has been studied and found, in general, to depend very little on the underlying type of heart disease, but, in varying degree, on the precipitating cause of failure, the patient's age, the degree of clinical cardiac enlargement, and the presence or absence of complications.

An additional analysis of the case histories of seventy-seven known hypertensive patients and ninety known nonhypertensive patients with coronary thrombosis revealed that a greater percentage of hypertensive patients will develop congestive heart failure than will the nonhypertensive, and consequently the prognosis is poorer for the former group of patients when coronary occlusion occurs. Once failure develops, however, the outcome is the same for those with or without antecedent hypertension.

AUTHORS.

Crafoord, C., and Jorpes, E.: *Heparin as a Prophylactic Against Thrombosis.* *J. A. M. A.* 116: 2831, 1941.

In 325 cases involving postoperative treatment with heparin, symptoms of thromboembolic complications did not arise. In a control series of 1,111 similar cases such complications occurred in 9 per cent.

The patients selected were in both series over thirty-five years of age and submitted to operations on the gastrointestinal tract, the biliary system or the urinary passages or to major operations for hernia and varices.

Reference is made to another series of eighty-eight patients with gynecologic disorders operated on for myoma or prolapsus uteri without any thromboembolic complications. In the control series of 1,054 cases there were complications in 4 per cent.

The heparin used had a strength of about 70 per cent of the pure mucoitin trisulfuric acid. It was given as a 5 per cent sterile solution in intermittent intravenous injections four times a day. The ordinary dose was 50 plus 50 plus 50 plus 100 (or 75 plus 75 plus 75 plus 125) mg. daily, started four hours after the operation. The treatment was continued for five to ten days.

AUTHORS.



Ebert, R. V., and Stead, E. A., Jr.: *Circulatory Failure in Acute Infections*. J. Clin. Investigation 20: 671, 1941.

Eight patients with circulatory failure produced by acute infection were studied. Five patients had lobar pneumonia; four of these had bacteremia. There was one case of streptococcal septicemia, one of staphylococcal septicemia, and one of bronchopneumonia without bacteremia. The circulatory failure was characterized by a decrease in peripheral blood flow and a fall in arterial pressure.

Measurements of the hematocrit level, the serum protein concentration, and the plasma volume showed no evidence of significant hemoconcentration or diminished blood volume.

The venous pressure determined before transfusion was normal.

Elevating the foot of the bed did not improve the circulation.

Transfusions of whole blood, or plasma, or the infusion of 10 per cent glucose in saline until the venous pressure rose did not produce any improvement in the circulation.

Blocking the ulnar nerve caused the ulnar side of the hand and the fourth and fifth fingers to become warmer than the other fingers. This showed that the vasoconstriction in the hand was neurogenic in origin.

The circulatory failure in these cases does not have the same mechanism as that of hemorrhage or traumatic shock, because the plasma volume is not decreased and transfusions are not beneficial. It is not caused by venous pooling, because filling the venous system does not improve the circulation.

The entire cardiovascular system appears to be damaged by the infection. The absence of congestion and the fact that the venous pressure is not increased may be explained by simultaneous injury to the heart and loss of venous tone.

Improvement in the circulation occurs only when the infection is brought under control. Therapy should therefore be directed toward overcoming the infection rather than attempting to treat the circulatory failure itself.

AUTHORS.

Cole, G. C.: *The Conus Arteriosus and the Pulmonary Artery*. Am. J. Roentgenol. 45: 32, 1941.

An improved method of visualization of the pulmonic conus and the pulmonary artery, as well as the left hilum region, is described. That it has definite advantages over the standard methods of visualization is clearly demonstrated.

The method is based primarily upon a knowledge of the anatomic and histologic structures of the conus arteriosus and proximal portion of the pulmonary artery, as well as upon mechanical changes, namely, rotation of the conus on its horizontal axis so that its greatest length and depth will be horizontal to and traversed by the central rays, and also upon exaggeration of structures by bringing them farther away from the screen.

AUTHOR.

Mohs, F. E., Sevringhaus, E. L., and Schmidt, E. R.: *Conservative Amputation of Gangrenous Parts by Chemosurgery*. Ann. Surg. 114: 274, 1941.

A method is described for chemically fixing gangrenous tissue to prepare it for conservative amputation. The technique consists of rendering the surface keratin permeable to zinc chloride by applying a keratolytic such as dichloroacetic acid. Zinc chloride paste is then applied to the involved area in a layer 2 mm. thick, in order to fix the lesion to a level somewhat proximal to the limits of the visible gangrene. The material is held in place by a cotton dressing, and excessive drying is avoided by covering with a second layer of cotton, spread with vaseline.

After about twenty-four hours the gangrenous area (usually a toe) has been fixed and can be amputated.

The extraordinarily favorable healing after this procedure made possible successful results in over 60 per cent of sixty-six conservative amputations in a series of cases which was essentially unselected in regard to circulatory efficiency. There were no breakdowns of the scars once healing had occurred, and there were no operative deaths in this series. The method enables the conservative treatment of gangrene to be extended to a much larger group of patients than was previously possible.

NAIDE.

Allen, Frederick M.: *Reduced Temperatures in Surgery. I. Surgery of Limbs.* Am. J. Surg. 52: 225, 1941.

The author outlines a method of amputation of extremities of patients with vascular disease with the use of refrigeration. The reduction of temperature enables the surgeon to use a tourniquet to obtain a bloodless field. Also, the refrigeration induces anesthesia of the extremity so that all the harmful effects of the usual anesthetics are avoided. A cold environment is valuable in preventing infection, aiding in healing, minimizing thrombosis, and reducing after-shock.

NAIDE.

Taylor, N. B., and Waters, E. T.: *Isinglass as a Transfusion Fluid in Hemorrhage.* Canad. M. A. J. 44: 547, 1941.

Because of the difficulty involved in obtaining large quantities of blood or serum for the treatment of hemorrhage, the authors looked for a substitute which would meet the rigid requirements of a transfusion fluid. A 7 per cent solution of fish gelatin or isinglass in 0.9 per cent saline was found to fulfill the specifications of a transfusion fluid.

As prepared from the sounds (air bladders) of fish by the method described, isinglass is soluble in water or saline, is without toxicity, and can be readily sterilized by raising its temperature to 100° C. for five minutes. It forms a perfectly clear pale yellow solution.

Experiments are reported in which a 7 per cent solution of isinglass in saline was capable of restoring the blood pressure after it had been lowered by hemorrhage and of saving the lives of animals which, had no treatment been instituted, undoubtedly would have died. These animals made a complete and uneventful recovery.

NAIDE.

Wood, G. O., and Blalock, A.: *Effects of Uncomplicated Hemoconcentration (Erythrocytosis).* Arch. Surg. 42: 1019, 1941.

Marked degrees of hemoconcentration unaccompanied by significant alterations in the blood volume have been produced experimentally by the removal of whole blood and the reintroduction of the red blood corpuscles together with additional ones from compatible donors. Rather marked hemoconcentration produced in this manner is compatible with life in experiments of the duration recorded and does not usually result in significant alterations in the tissues except for vascular engorgement. Whereas both hemoconcentration and reduced blood volume exert deleterious effects in the presence of shock, it is concluded that it is the decrease in the blood volume with the resulting anoxia that is responsible for most of the damage to the tissues. It should be emphasized that these experiments are concerned not with

chronic erythrocytosis but with temporary elevations in concentration, such as may occur in association with shock.

AUTHORS.

**Blalock, A., and Mason, M. F.:** A Comparison of the Effects of Heat and Those of Cold in the Prevention and Treatment of Shock. *Arch. Surg.* 42: 1054, 1941.

The effects of causing rather marked elevations or depressions of the body temperature of animals in shock as a result of hemorrhage or trauma have been determined. Significant elevations of temperature decrease the chance of life and shorten the period of survival. The application of cold does not increase the chance of survival but is accompanied with a lengthening of the survival of an animal with a low blood pressure. Significant elevations of temperature cause more disastrous effects than do depressions of similar degree.

AUTHORS.

**Ersler, I. L., and Blaisdell, I. H.:** Massive Hematuria Following Use of Heparin in Cavernous Sinus Thrombosis. *J. A. M. A.* 905: 927, 1941.

The intravenous administration of heparin produces a significant prolongation of the coagulation time, which is, in fact, a hemorrhagic diathesis. Consequently there may be produced dangerous bleeding in vital areas of the body. A patient with cavernous sinus thrombosis, treated with sulfathiazole and heparin, presented profound renal bleeding from which there were no serious sequelae. Bleeding from cerebral, pulmonary, or coronary vessels might conceivably result in disaster.

NAIDE.

**Rigdon, R. H., and Wilson, H.:** Capillary Permeability and Inflammation in Rabbits Given Heparin. *Arch. Surg.* 43: 64, 1941.

Heparin as used in these experiments has no effect on capillary permeability, the macroscopic development of inflammation, or the localization of leucocytes in areas of inflammation.

The phagocytosis of staphylococci by polymorphonuclear leucocytes in vivo apparently is not affected by heparin.

AUTHORS.

## Book Review

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**SURGERY OF THE HEART:** By E. S. J. King, M.D., D.Sc., F.R.C.S. (Eng.), F.R.A.C.S., Major, A.A.M.C., Honorary Surgeon to Out-Patients, Royal Melbourne Hospital. Williams and Wilkins, Baltimore, 1941, 728 pages, 268 illustrations, \$13.50.

This book was prepared as a dissertation for the Royal College of Surgeons, in 1938. It was granted the Jacksonian prize. I believe that many physicians would like to have it in their libraries. It contains an extensive review of the literature up to 1937. The book is a good reference work, and can be recommended to those surgeons who are exploring any of the fields which it covers.

A large part of the book is devoted to a discussion of nonsurgical topics. Undoubtedly this is done for the purpose of making the book approach completeness, because these discussions have little or no relationship to surgery. There is a chapter on developmental abnormalities of the heart. However, the only developmental abnormality that can be treated by operation, namely, patency of the ductus arteriosus, receives one paragraph of discussion, and the operation is not illustrated. The chapters on anatomy, physiology, and pathology appear to be well written, but I question the relationship of this material to surgery. For example, under the subject of histology one finds a discussion of the muscle fiber, transverse striations, the sarcomere, the form of the striations, intercalated discs, protoplasmic organoids and inclusions, the sarcolemma, the nucleus, and so on. The chapter on pathologic physiology is good. However, when we turn to the practical application of some of this information on pathologic physiology, there is something to be desired. Resuscitation of the heart is not presented as a practical problem. The author does not tell the surgeon precisely what to do if the ventricles should go into fibrillation during an operation on the heart.

In his chapter on electrocardiography the author has this to say: "There can be no doubt, especially recently, that many investigators have been trying to give to small changes a significance which they do not possess. Every study requires the most careful and critical control before it can be accepted." The chapter on the surgical approach to heart disease is good. The chapter on injuries to the heart is exceptionally good. The author discusses abscess of the heart, chronic myocarditis, rheumatic fever, tuberculosis of the myocardium, syphilis of the heart, actinomycosis of the myocardium, enlargement of the heart, decompression of the heart, displacements of the heart, vascular disease, calcification, tumors of the heart, parasitic diseases, hydatid disease, coronary occlusion, paravertebral injections, total thyroidectomy, aneurysm of the coronary arteries, and rupture of the coronary arteries. Valvular disease is discussed in reference to the possibility of operative treatment. Diseases of the pericardium embrace 141 pages.

The following quotation is from page 628: "Constrictive pericarditis must be distinguished from other (I) pericardial disease, and (II) from other conditions. (I) The confusion between various forms of pericarditis is demonstrated excellently in the literature. A brief consideration of the essential differences due to the site of the fibrosis, as described above (p. 602), however, indicates the differentiating features. Thus evidence of extra-pericardial adhesions to the chest wall is absent. Such adhesions may be present, but the density of the pericardium, limiting cardiac movement, prevents their becoming apparent clinically. Broadbent's sign therefore

is absent (Turk). The heart is much smaller than in mediastinopericarditis, valvular lesions are usually absent, and there is no history of rheumatism." This is an example of the confusion that exists in the literature, and the author has failed to clarify the subject.

The author makes a plea for opening the pericardium when the heart is enlarged. A quotation from page 642, on the restrictive action of the pericardium on the enlarged heart, is as follows: "The study of this condition has been given impetus in recent years by the observations of Felix. He has emphasized the lack of adequate concomitant stretching of the pericardium in some cases of cardiac enlargement so that it is tightly stretched over the heart. Although his explanation of the symptoms—that there is a relative compression of the right ventricle—is not in accord with other observations on the physiological action of the heart, his observations are of the greatest importance. The treatment suggested—an incision in the pericardium—allows the heart to bulge and is followed by considerable relief of symptoms and signs. This improvement has been observed by the writer in several cases.

"Experimental work on animals, especially the racing greyhound, is of special significance in this regard. Some animals develop a marked diminution of cardiac reserve shown by enlargement of the heart and, after exercise, by cyanosis (most easily observed in the tongue), dyspnoea and an easily observed thrill over the apex beat. Such animals are unable to perform as well as formerly and indeed may collapse before finishing an ordinary course. They recover from the effect of exercise much more slowly than do normal dogs, often requiring two to three times as long. Wide incision of the pericardium, which is followed by bulging of the heart into the opening, is followed by very great improvement so that the animal is able once more to compete with its fellows. Such observations have been made by O'Shaughnessy and McCunn. The writer has been astonished on several occasions by the degree of improvement obtained.

"This experimental work has an important bearing on human cardiac disease and there appears to be a proportion of cases of cardiac decompensation, as the writer found, which are improved by the procedure. . . ."

It seems to me that the writer is using strong generalities in recommending this operation. I believe that the reader would like to have actual observations on patients concerning the results. If the author is correct, the reader would like to have a program of action, so that his patient with cardiac decompensation can be given the benefit of this operation. I believe that he would also like to have the experiments and their controls, so that he could arrive at his own conclusion concerning the subject. This operation has not become established, and a practical program of action in reference to these patients is not found in this book.

The book has much to recommend it. It seems to me that the author of a monograph on surgery of the heart must expect to encounter difficulties and pitfalls. The total experience in this field is not great. There are few surgeons who have done as many as fifty operations on the human heart. It can readily be understood that if the experiences are few, the conclusions can be expected to be indefinite and variable.

CLAUDE S. BECK.

## In Memoriam

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STEWART RALPH ROBERTS

1878-1941

Stewart Ralph Roberts, Professor of Clinical Medicine at Emory University, Atlanta, Georgia, died at his home on April 14, 1941. In 1938 he had an extensive cardiac infarction from which he made a very slow recovery, but, for the past two or three years, although physically incapacitated to a great extent, he was able to carry on part of his teaching in the medical school and a limited consulting practice.

He was born at Oxford, Georgia, near the campus of Emory College, on Oct. 2, 1878. He was the son of the Reverend J. W. Roberts and Clifford Rebecca Stewart. His father was a graduate and trustee of Emory College. His grandfather, Joseph S. Stewart, graduated from Emory College with second honor, and for several years was also a trustee of this institution. His great-grandfather Starr, in 1849, was one of the original contributors to the establishment of Emory College.

With such a heritage it is easily understood why, during his entire life, Stewart Roberts manifested a great interest and love for Emory College, and was always interested in every opportunity that afforded advancement or improvement for this school. This interest was not only of paramount consideration during his college days, but throughout his entire professional career, when much of his interest was transferred from the academic to the medical department.

In 1894 Dr. Roberts first entered Emory College at Oxford, Georgia. After two years of college work he decided to abandon this field of endeavor and to undertake the study of medicine. In 1896 he began the study of medicine at the Southern Medical College, which, in 1898, became the Atlanta College of Physicians and Surgeons, from which he graduated in 1900. After his graduation in medicine he became dissatisfied with his literary training, and, in the fall of 1900, he returned to Emory College and for two years devoted himself to further academic study, graduating in 1902 with the degree of B.S.

The following year he became Professor of Biology at his Alma Mater. Several years later he did postgraduate work at the University of Chicago and also at the Harvard Medical School. He taught biology at Emory College from 1902 until 1906. Resigning this professorship, he moved to Atlanta and became Professor of Physiology at the Atlanta School of Medicine, where he taught from 1906 until 1910. Shortly after

he assumed the professorship of Physiology, the Atlanta Medical College and the Atlanta College of Physicians and Surgeons combined to form the Medical Department of Emory University. During this period of reorganization Dr. Roberts became Professor of Clinical Medicine, a chair which he occupied with dignity and honor until his death.



STEWART RALPH ROBERTS

Many honors were conferred upon him by his colleagues. He was at one time President of the Fulton County Medical Society, the Southern Medical Association, Vice-President and member of the Board of Regents of the American College of Physicians, a diplomate of the American Board of Internal Medicine, Physician to Emory University Hospital, Consulting Physician to the Henry Grady Hospital, President of the American Heart Association, and Vice-President of the Medical Association of Georgia.

During the last World War he was a Lieutenant Colonel in the Medical Corps, in command of the Base Hospital of Camp Jackson, Columbia, South Carolina. In this particular capacity he rendered most distinguished service.

He was a member of the Kappa Alpha, Omicron Kappa Delta, Phi Beta Kappa, and Alpha Omega Alpha Societies.

His ability as a writer and as a speaker is well known. His many contributions to the advancement of medical science have been published in the leading medical journals of this country. His book on pellagra, published in 1912, was a very authoritative statement of our knowledge

of this disease at that time. Very few physicians have ever equalled or surpassed Dr. Roberts in his ability to speak authoritatively and convincingly before medical gatherings, and very few organizations have not had the privilege of hearing his voice.

For many years he had a great interest in cardiovascular diseases, and, during 1933 and 1934, while President of the American Heart Association, he was most helpful in the deliberations and counsel of this body.

He is survived by his wife, the former Miss Ruby Holbrook, and three sons. A host of friends and associates will miss his counsel, his advice, and his kind and generous philosophy.

JAMES E. PAULLIN.



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The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

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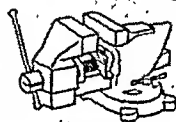
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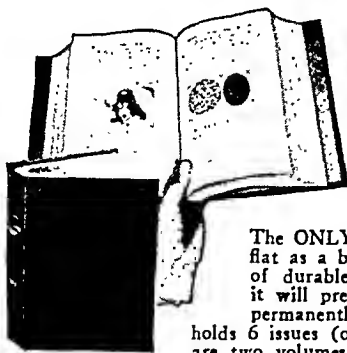
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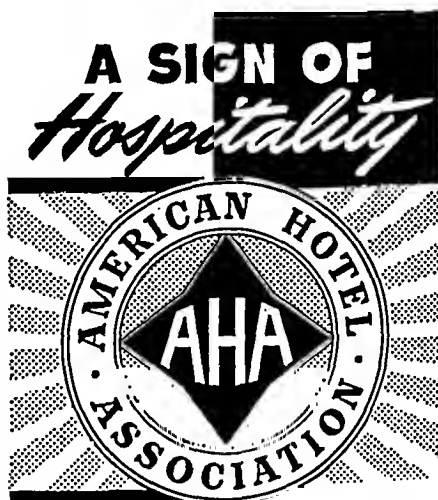
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# American Heart Journal

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## Original Communications

### PERIPHERAL CIRCULATORY FAILURE

ALFRED BLALOCK, M.D.  
BALTIMORE, MD.

THE honor of being asked to give the George E. Brown Memorial Lecture for 1941 is appreciated very greatly. Brown, who, like Banting, and others, left a small community in order to put his new ideas to a more rigid test, shall be remembered as a notable contributor to the art and science of medicine. It is particularly fitting that this society should honor his memory, because his greatest interest was in the field of vascular disease.

To cover the entire field of shock, or peripheral circulatory failure, even if I were capable of performing the feat, would be obviously too great a task for this brief lecture. Much that might be said must be omitted, and for this I beg your forgiveness. A detailed consideration of the subject can be found in monographs by Cannon,<sup>1</sup> Moon,<sup>2</sup> Seudeder,<sup>3</sup> and Blalock,<sup>4</sup> and in a recent review by Harkins.<sup>5</sup>

It is agreed that Cannon<sup>1</sup> is correct in his statement that definition is not a prime requisite in such a complex as shock. Granting that no definition is entirely adequate, one may state that shock is a condition of peripheral circulatory failure brought on by a discrepancy between the volume of circulating blood and the size of the vascular system and leads to a deficient blood supply to the tissues of the body. This discrepancy may be due to a reduction of the blood volume, or to an increase in the capacity of the vascular system, or to both. The combination of alterations almost certainly occurs more often than has been suspected.

Even though definition is not a prime requisite, it is important that the clinical picture should be familiar to all, and careful descriptions are available. There is no difficulty in recognizing the fully developed condition, but, unfortunately, there is no known certain index as to the condition of the circulation in early or incipient shock. Determinations of the pulse rate and of the concentration of the erythrocytes are usu-

George E. Brown Memorial Lecture, Seventeenth Meeting of the American Heart Association, Cleveland, Ohio, May 31, 1941.

Received for publication Sept. 6, 1941.

ally of value in this respect, but either or both may be misleading. Unfortunately, the arterial blood pressure usually does not decline greatly until after rather marked changes in the circulation have occurred. Even though the arterial pressure is not a good guide to the condition of the circulation in incipient shock, it is the best available index to the state of affairs in shock that is more fully developed.

It is important to remember that not all declines of blood pressure are of the same significance. There is a vast difference between two patients, both with a blood pressure at the critical level, when one has cold extremities and the other has warm or only slightly cool extremities. The patient who has a low arterial pressure and cold extremities usually has arterial vasoconstriction secondary to a significant reduction in the blood volume. The prognosis is usually very grave unless a sustained elevation of the decreased blood volume can be brought about by appropriate therapy. On the other hand, the situation is not so grave when the person with a low blood pressure has no significant reduction in blood volume. Vasodilatation, instead of vasoconstriction, is present, and the condition will usually clear up spontaneously or will respond to vasoconstrictor drugs. Some patients present a combination of the two types, i.e., both a diminution of the blood volume and vasodilatation are present. These various types will be discussed in more detail subsequently.

This paper is concerned in the main with the type of disturbance in which there are a diminution in the blood volume and vasoconstriction; in other words, so-called traumatic, or wound, or secondary, or hemogenic shock.

#### TERMINAL ALTERATIONS IN SHOCK

There are many causes of shock, but, regardless of the cause, the terminal alterations are very much the same, providing there is an inadequate supply of blood and oxygen for the tissues for an extended period. If a patient dies almost immediately as a result of bleeding from a wound of a large vessel, it is only natural that the tissues of the body should appear anemic at autopsy. On the other hand, if death occurs several hours later, following an extended period of anoxia, a different picture is presented. It simply happens that the anemic appearance of the tissues is encountered more frequently because patients who succumb as a result of uncomplicated hemorrhage from a large vessel usually do so almost immediately.

A prolonged period of an inadequate supply of blood to the tissues was produced in unanesthetized animals by the simple withdrawal and replacement of blood.<sup>6</sup> There was no bodily trauma and no toxins were introduced. After maintaining the blood pressure and blood volume at low levels for several hours, the animals died *despite the fact that more blood was introduced than had been removed*. An increase in the concentration of the blood occurred, and capillary congestion and hemor-

rhage were found on examining the tissues. These changes, which have been believed to indicate "toxemia," may be simply the result of long-standing tissue anoxia.

The particular significance of these experiments is that they remove some of the mystery with which shock has been surrounded. The results throw no light on the question whether the etiological agent in different cases is the absorption of toxins or noiceptive nervous stimuli, or the local loss of blood and fluid or other causes, but they show that the alterations usually encountered in secondary shock can be caused by a simple, marked reduction of the blood volume of unanesthetized animals. It is not necessary to assume that the vital spirits have been exhausted, or that the body of the patient in shock is a big wheel, as some observers have contended. It is important to realize that a prolonged, inadequate supply of blood and oxygen, whether due to the loss of whole blood or plasma, and whether the loss is local or widespread, will result in alterations in the tissues of the body, providing the subject lives long enough for the changes to occur.

#### PATHOGENESIS

There should be little dispute as to the nature of the terminal manifestations of shock, providing one takes into account the length of time that the circulation has been inadequate, but there is a justifiable difference of opinion as to the cause of the diminution in the blood volume. In the first place, there are many causes of shock, and the same cause is not predominant in all cases. This fact does not minimize the importance of ascertaining the main initiating agent or agents in different types of shock, for it is only in the early stages that distinctive characteristics can be identified, and it is only in the stages before irreversible changes have occurred that treatment is effective.

The problems of pathogenesis and treatment are made more difficult because a standard method for producing a given degree of peripheral circulatory failure is not available. There is no scarcity of methods for producing shock, but one cannot predict with certainty the effects of the removal of a certain quantity of blood, or of the injection of a given dose of histamine, or of the infliction of a known number of blows with a blunt instrument. In other words, there is such a large individual variation in the reactions of different animals to the various shock-producing measures that the interpretation of studies on pathogenesis is difficult, and it is almost impossible to evaluate the effectiveness of various therapeutic procedures unless the agent causes dramatic changes.

To be more specific, normal unanesthetized dogs vary somewhat in their responses to the removal of large quantities of blood. The same is true of the effects of trauma on anesthetized dogs. The skeletal muscles of some animals become macerated very easily when severe trauma

is inflicted, whereas those of other animals are very resistant to trauma. As for the injection of toxic agents, one dog may survive several times the dosage that is fatal to another healthy dog of similar size. As stated previously, this renders the study of the problem of therapy particularly difficult.

The replies to a questionnaire which was sent recently to various investigators in this field indicate that there is no agreement as to the best method of producing shock, and most of them expressed the need for a standard procedure. As a matter of fact, it would appear that we are in need of a standard animal rather than a standard procedure, for it is the individual variations of animals that complicate the interpretation of results. The same may be said, however, of the study of most problems. On the other hand, one may take consolation from the fact that man varies as greatly as the experimental animal in his response to hemorrhage, trauma, and infections, and the individual factor is inescapable.

In spite of the individual variation in response to hemorrhage, I believe that the most easily controlled method for the production of shock is the removal of blood. The most serious objection to the method is that most persons in shock have lost a greater proportion of plasma than of erythrocytes. Due to the fact that all dogs of the same weight do not react identically to the loss of the same quantity of blood, it appears to me that one should remove blood (0.5 to 1 per cent of body weight) at thirty-minute intervals until a sustained decline in arterial pressure to approximately 75 mm. Hg has resulted. In other words, one should use as the standard the reduction of the blood pressure to a given level, rather than the removal of a predetermined quantity of blood. If the latter scheme is used, one should follow the advice of Gregersen, i.e., use a standard breed dog, ascertain the blood volume of each dog, and remove a certain percentage of the blood volume.

If one wishes to cause traumatic shock, it appears to me that traumatization of one of the two posterior extremities is the method of choice. As Cannon<sup>1</sup> has pointed out, the opposite extremity can be used as the control. The same may be said of the use of one side of the body in studies on burns. For the study of the effects of toxic substances, the use of histamine presents certain advantages. In any case, whether one uses these or other available methods, one should remember that the effects of all anesthetic agents are not identical and that this factor should be controlled as accurately as possible. Furthermore, if the experiments are of several days' duration, and if the use of an anesthetic agent is necessary, the ill effect of the agent may be greater than that of the procedure which one is employing.

In spite of the fact that the methods leave much to be desired, certain pertinent observations have resulted from their employment and from clinical studies. Certain of the many theories of shock have been more

or less discarded in recent years, whereas greater attention has been focused on others. In most instances, however, it has been a question of assessing the relative merits of the various theories, rather than entirely excluding some of them. For example, it appears fairly definite that fat embolism may, and does, cause shock, but it is one of the more infrequent etiological agents. Rated in order of increasing importance in explaining the initial alterations in shock, in my opinion, are (1) the hypothesis of toxemia, (2) the theory of disturbed function of the nervous system, and (3) the theory of the local loss of blood and fluid. It should be emphasized that this statement applies to initiating rather than sustaining factors, for it is generally recognized that a general increase in capillary permeability takes place after the blood volume and blood pressure have been depressed for a considerable period. Additional consideration will be given to these three theories.

#### THEORIES

##### *1. Toxemia Theory*

The toxemia theory is founded, in the main, upon indirect evidence gained in the study of human beings and animals. No attempt will be made to review the great bulk of evidence which supports this theory. It was the prevailing theory at the conclusion of the last war, and it still has many supporters. There is no doubt that snake venom and many other toxins, as used by Moon<sup>2</sup> and others, will produce shock, but this does not prove that such products are the cause of traumatic shock. In regard to the original experiments which contributed the main evidence for the toxemia theory, Dale<sup>7</sup> stated several years ago: "With regard to the possible role of histamine, we know now what we did not know then, that of all the major tissues of the body, the muscles contain least of that substance. Whatever else it may have been, the shock following the Bayliss-Cannon limb trauma was not histamine poisoning." This statement, however, should not be interpreted to mean that there may not be slowly acting decomposition products which exert ill effects. The statement regarding the toxemia theory which Cannon<sup>8</sup> made a few years ago appears to be a very sound one. "And even though we may not have devised experiments which demonstrate the presence of any shock-inducing chemical agent, there still remains the clinical testimony, mentioned above, that material absorbed from dead and dying tissues and distributed in the organism may be toxic—so toxic as to play a role in lessening the quantity of circulating blood. It seems unwarranted, therefore, to exclude from further consideration the view that traumatic shock may be, at least in part, a resultant of toxemia."

It is my impression that toxemia has not been excluded as a cause of shock following trauma, but I do not believe that it is a frequent initiating factor. In discussing the etiology of shock in association with



burns, Aldrich<sup>9</sup> stated that, when there is no infection, there is no toxemia. Even though I agree in the main with Aldrich, it is my opinion that the action of toxins, unaccompanied by infection, has not been excluded as a cause of some of the ill effects. At the same time, the evidence<sup>10</sup> indicates that the main cause for the reduction in the blood volume in the first two days after a burn is the local loss of plasma. This is particularly important because it is known that most fatalities which follow burns occur in the first two days. These statements are not meant to imply that toxemia is not a cause of shock, but rather that it is probably not a frequent initiating factor.

## 2. *Nervous Theory*

The nervous theory has not received the attention in recent years which its importance deserves. It is a particularly difficult viewpoint to attack experimentally because anesthesia is a necessary prerequisite to the infliction of trauma, and the responses are altered somewhat by the administration of an anesthetic agent. The various factors which may affect vascular tone were admirably presented by Cannon<sup>11</sup> in the first George E. Brown Memorial Lecture, and no attempt will be made to consider them in detail in this lecture.

Until relatively recently, the most important theory of the neurogenic production of shock was that the vasoconstrictor center was exhausted. During the past twenty-five years a number of observers have found that this is not the case, that the center will react to stimuli, and that the arteries are constricted in the earlier stages of secondary shock. It is a new idea, expressed in particular by Freeman,<sup>12</sup> that overstimulation of the sympathetic adrenal system is a frequent cause of shock. It has been pointed out that fear, anger, pain, cold, and mental stress cause stimulation of the sympathetic system. It is known that vasoconstriction is the compensatory response to hemorrhage. Although they admitted that sympathetomized animals withstand hemorrhage less well than normal ones, Freeman and his associates<sup>13</sup> found that the former type of animal is better able to tolerate prolonged depression of the blood pressure. Freeman is of the opinion that, in the production of shock, the activity of the sympathetic system causes intense vasoconstriction, peripheral asphyxia, and capillary dilatation. This theory has much to commend it, but it remains to be shown that uncomplicated vasoconstriction alone will result in shock. It is not vasoconstriction, per se, but rather the diminution in the blood flow to the tissues that results in disastrous changes. Patients and animals with hypertension may have intense vasoconstriction, but none of the manifestations of shock are present. The role of vasoconstriction in the causation of shock is probably that of an augmenting agent, rather than that of a main initiating factor. It is difficult to believe that the body is provided with a protective mechanism against hemorrhage which so readily results in harm when its aid is most needed.

It is believed that stimulation of afferent nerves may cause inhibition as well as stimulation of the sympathetic system. O'Shaughnessy and Slome<sup>14</sup> found that it was more difficult to produce shock by mechanical injury to an extremity if the nervous pathways were blocked. If this observation is correct, the question remains whether the anesthesia is protective because of its effect on excessive stimulation or on inhibition of the sympathetic system. At any rate, clinical experience indicates that the induction of spinal anesthesia after a severe crushing injury of the legs is contraindicated. A number of observers, including Cressman and Blalock,<sup>15</sup> have been unable to confirm most of the experimental results of O'Shaughnessy and Slome. They reported a barrage of impulses from the injured part, but Cressman and Benz<sup>16</sup> observed similar impulses on the nontraumatized side. It must be emphasized, however, that the failure to demonstrate with certainty the presence of nociceptive nervous stimuli does not exclude the possibility that the nervous system is an important agent in the causation of shock. It is my impression, however, that it is concerned, in the main, in the genesis of so-called reflex, or primary, shock.

It may not be out of place at this point to mention the fact that the explosion of a bomb may cause death, even though the person is not struck by shrapnel or debris. Hadfield and his colleagues<sup>17</sup> reported ten such cases. In three of these a fatal degree of saturation of the blood with carbon monoxide was found. In two the cause of death was compression asphyxia. In each of the ten cases some degree of capillary hemorrhage into the lung was found. In the four cases in which death was considered to be due entirely to the effects of blast, there was free hemorrhage in large pulmonary areas. They found that the amount of blood extravasated into the lung varied considerably. They are not of the opinion that the pulmonary injury itself could fatally embarrass the circulation. "It seems more likely that blast produces death by interfering with some vital tissue or centre in which, from the extreme rapidity of action, structural changes are unlikely to be found." The results of recent experiments on this problem are of interest.

Zuckerman<sup>18</sup> exposed animals at various distances to blast. The most outstanding lesion was bilateral pulmonary hemorrhage which varied in degree according to the distance of the animals from the charge. They found that it is the pressure wave of blast which bruises the lungs by its impact on the body wall and that this effect can be prevented or diminished if the body is clothed in a suitable material which is able to take up and disperse the pressure wave. Denny-Brown and Russell<sup>19</sup> found recently that cerebral concussion results not from the intensity of the blow on the head but from sudden acceleration caused by the blow. These observations may be pertinent in explaining the effects of blast. If the head is prevented from moving when struck, the phenomenon fails to occur. Acceleration in movement may result in death with-

out macroscopic lesions of the brain stem. They concluded that the nervous effect of a blow is thus due to the physical acceleration directly transmitted to each and every center. In discussing this subject, Fulton<sup>20</sup> stated that the microscopic causes for the symptoms are still obscure but no doubt have to do with some basic intracellular disorganization of the neuron. It is obvious that further work on this interesting condition is indicated.

### 3. *Local Fluid Loss Theory*

There is much evidence that local loss of blood and fluid is a frequent and important initiating factor in the causation of shock. It was shown by me<sup>21</sup> and by Parsons and Phemister<sup>22</sup> that the shock which follows severe trauma to an extremity is due, in the main, to the local loss of blood and fluid. The duration of these experiments was hours, rather than days, and the results do not exclude the possibility of action of other agents in injuries of longer duration. At the same time, these experiments were of approximately the same duration as those which furnished the best experimental evidence for the toxemia theory. Although he admitted that local loss of fluid is the most important cause of shock in injuries of this type, Best<sup>23</sup> stated that the volume of the loss is not sufficiently great in all experiments to account for the peripheral circulatory failure. It seems only fair in this connection to repeat that some dogs, even unanesthetized ones, will tolerate the removal of only a relatively small quantity of blood. Anesthesia is necessary for the studies on trauma, and this may in part be responsible for some instances in which death occurs despite the fact that the local loss of fluid in response to trauma is not great enough by itself to account for the decline of blood pressure.

Freedman and Kabat<sup>24</sup> and Cullen and Freeman<sup>25</sup> have found that shock may be produced by traumatization of extremities which are bound by tape in such manner that the local loss of fluid is restricted. In most of these experiments the local loss of fluid was not sufficiently great to account for the peripheral circulatory failure. The explanation for this is not apparent. It seems only fair to state, however, that the clinical implications are not very great because patients who are injured do not have their extremities protected against the local loss of blood and fluid in this manner. The experiments may be of significance in connection with patients who are pinned beneath objects, as in some air raids, from which they cannot escape.

The local loss of fluid which accompanies severe trauma consists, in the main, of whole blood, although there is a somewhat larger proportion of plasma than of erythrocytes. Milder injuries result primarily in the loss of plasma. Burns are a striking example of this type of injury. The protein content<sup>26</sup> of fluid which accumulates at the site of a burn is practically identical with that of the plasma in the blood vessels. In burns of approximately twenty-four hours' duration,

I found that the local loss of plasma was sufficient by itself to account for a reduction of the blood pressure.<sup>10</sup> It is not maintained that all deaths which follow burns are due solely to the local loss of plasma, but it is maintained that this loss is the most important cause of the shock which may follow a severe burn. This fact assumes added importance, when it is recalled, as Mitchiner<sup>27</sup> has emphasized, that 80 per cent of the deaths which result from burns occur within the first two days.

Although there are many instances of shock which cannot be explained by the local loss of blood and fluid, it is my impression that this loss is the most important and the most frequently encountered of the initiating factors which result in a decline of the blood volume and in traumatic shock. Points in favor of this theory are that the etiological agent is measurable under controlled conditions, and one does not have to assume the presence of some substance such as a hypothetic toxin. Furthermore, it is to be hoped that such a theory is correct from a therapeutic viewpoint, in that replacement treatment affords a better outlook than combating a hypothetic toxin or some other unknown agent.

At the conclusion of the last war, great stress was placed on the institution of measures which would result in a reduction of the absorption of toxins. It is only fair to state that therapy included the intravenous administration of blood and blood substitutes. At the same time, this latter form of therapy was used only sparingly, as compared with today. The best clinical study of shock that has been reported recently is that of Whitby,<sup>28</sup> and associates, of Bristol, England. They report, in detail, twenty-four cases of severe secondary shock which resulted from injuries in air raids. A typical example is the following, in which therapy included the administration of three pints of plasma and four pints of whole blood.

“Case 3. Male, aged 24. Seen 3½ hours after injury. Multiple small injuries of back, legs and arms, gaping hole in right buttock nine inches in diameter, buttock almost completely removed, perforating wound left wrist joint. Morphia gr. ¼ 1¼ hours after injury. Warmed with electric blanket for 1¼ hours before transfusion. Mentally clear, pain ++, thirst +, pallor ++, cyanosis ++, sweating slight, temperature 95° F., pulse 82, blood pressure 40/30, hemoglobin ear 120%, vein 100%, hematocrit 43%.

“After 1 pint plasma in 20 minutes pulse 100, blood pressure 70/40. After 2nd pint plasma in 20 minutes pulse 120, blood pressure 80/45. After 3rd pint plasma in 20 minutes pulse 128, blood pressure 100/55, hemoglobin, ear 80%. Greatly improved but pallor still extreme; 1 pint blood given in 30 minutes, pulse 120, blood pressure 100/60. Started bleeding from buttock; 1 pint blood given in 30 minutes. During operation of debridement at which much bleeding 2 further pints blood administered, each in 15 minutes. Anaesthetic G.O.E. After operation pulse 110, blood pressure 112/70. After 24 hours general condition good; pulse 120, blood pressure 115/80, hemoglobin 78%.”

Several points which were made by Whitby and his associates are worthy of consideration in greater detail. They found that the blood pressure is the most reliable measurable indication of the severity of

secondary shock and that other clinical manifestations are variable and not quantitative. The pulse rate was unreliable. It was noted that the cardinal symptoms of shock can be present without much hemoconcentration. In regard to the cause for the decline of blood volume, they make the following statement: "In all cases seen by us it has appeared that the loss of blood volume can be accounted for by external loss and by extravasation into the injured area. In no case has there been evidence to suggest loss of plasma in regions remote from a seat of injury." These observations afford strong evidence in favor of local loss of blood and fluid as an important agent in the causation of traumatic shock. At the same time, I wish to emphasize again the point that there are other causes of shock.

#### CLASSIFICATION OF PERIPHERAL CIRCULATORY FAILURE

For purposes of clarity, this consideration will be from the viewpoint of pure types and mixed types, admitting that pure is a relative, rather than an absolute, term.

*Pure Types.*—The terms<sup>29, 30</sup> that are used to designate the different types are hematogenic, neurogenic, and vasogenic. Synonyms for hematogenic are secondary, or traumatic, or wound shock, and it is with this type that this paper is mainly concerned. There is a decrease in the blood volume, vasoconstriction, a decrease in the cardiac output, and subsequently a decline in the blood pressure. The local loss of blood and fluid is the most frequent initiating factor. Examples of this type are external hemorrhage, bleeding into the pleural and peritoneal cavities, loss of blood and fluid into the tissues as a result of trauma, and loss of plasma at the site of a burn.

In the neurogenic type there is vasodilatation which is dependent on diminished constrictor tone as a result of influences acting through the nervous system. Examples of this are so-called primary shock and the conditions which may result from transection of the cervical cord or from the injection of an excessive amount of a spinal anesthetic agent. In the vasogenic type the vasodilatation is produced by agents which act directly on vessels. The injection of histamine produces this type of alteration.

*Mixed Types.*—As stated previously, many instances of shock are very complicated, and a number of causes are responsible. It is not always possible to ascertain which is the most important of the initiating factors. For example, many different factors may enter into the production of the shock which may accompany surgical operations. Included among these are the pre-existing illness, dehydration, primary psychogenic and neurogenic depressor reactions, hemorrhage, sweating, anesthesia, loss of plasma from exposed surfaces, pooling of blood in damaged areas, infection, and toxemia. Similarly, the mechanism of the peripheral circulatory failure which may result from peritonitis may

be very complicated. The stagnation of blood in dilated blood vessels in the enormous peritoneal surface, the loss of fluid from these vessels, and toxemia are probably the main contributing factors to the peripheral circulatory failure. A diminution of blood volume as a result of dehydration is undoubtedly one of the factors of importance in the causation of the shock which may occur in diabetic acidosis.

Peripheral circulatory failure is an ever present danger in severe, acute infections. Except in rheumatic fever and diphtheria, failure of the peripheral circulation, rather than cardiac insufficiency, is the more frequent cause of death. It is only the previously damaged heart that is likely to fail during an acute infectious disease. Unfortunately, information concerning the mechanism of peripheral circulatory failure in the acute infections, such as pneumonia and typhoid fever, is very meager. It is likely that there is a diminution in the circulating blood volume. This may be due to injury to the capillaries by toxic substances, with consequent stagnation of blood in dilated vessels, and extravasation of plasma.<sup>31</sup> Anoxemia alone may be responsible for the injury to the capillaries. The loss of plasma into the pneumonic areas is probably in part responsible for the peripheral circulatory failure of pneumonia. It is obvious that our information on the nature of the peripheral circulatory failure in acute infections is very meager and that additional studies are indicated.

#### ACUTE FAILURE OF THE HEART

Many of the clinical features of peripheral circulatory failure may be produced by heart failure of sudden onset. There may be considerable difficulty, for example, in determining whether a patient with abdominal pain and the clinical picture of shock has coronary thrombosis or circulatory failure of peripheral origin. Harrison<sup>30</sup> has stated that, from the viewpoint of pathogenesis, the symptoms of heart failure belong to two groups—those due to engorgement resulting from backward failure and those due to inadequate cardiac output, or forward failure. In acute failure of the heart, forward failure dominates the picture and evidences of passive engorgement are not very prominent.

Since the methods of treatment of central and of peripheral circulatory failure are different, a correct diagnosis is very important. In this differentiation, direct and indirect evidence is helpful. Direct evidence of heart failure includes the presence of venous engorgement or signs of pulmonary congestion. These alterations are not very marked in the acute stage. Abnormal fullness of the veins excludes shock and indicates heart failure. However, abnormal emptiness of the veins, which is always present in shock, may be found in heart failure if the congestion is limited to the pulmonary system. In the latter instance, dyspnea and orthopnea, usually, but not necessarily, associated with rales in the lungs, are observed. The patient with heart failure prefers the sitting

position; this is not true of the patient in shock. The indirect evidence consists chiefly of associated symptoms and signs pointing toward some likely cause of either peripheral circulatory failure or of heart failure. For example, the presence of peritonitis or intestinal obstruction is suggestive of circulatory failure of peripheral origin, whereas the manifestations of coronary thrombosis or of intrapericardial fluid point toward heart failure as the probable cause.

#### TREATMENT OF PERIPHERAL CIRCULATORY FAILURE

No attempt will be made to discuss the problem of therapy in detail. It is obvious that every effort should be made to prevent the development of shock. The avoidance of dehydration is one of the most important points in this connection. It has been estimated that the total amount of the secretion into the intestinal tract of an adult is approximately 8 liters per day. When it is realized that most of these secretions may be lost by persistent vomiting or diarrhea, and when it is further realized that the total volume of blood plasma is less than 4 liters, the importance of the replacement therapy becomes evident.

The single, most important therapeutic procedure in the treatment of traumatic shock consists of the intravenous introduction of whole blood, plasma, or serum. The vasoconstrictor drugs, which are useful in the therapy of neurogenic shock, are not indicated in secondary shock. In the combination of neurogenic and secondary shock, small doses of vasoconstrictor drugs may be helpful. Solutions of crystalloids are indicated in the treatment of dehydration, but large quantities of these should not be administered intravenously to patients who have sustained severe damage to their capillaries as a result of direct injury or anoxemia. The introduction of large quantities of noneolloidal solutions under these circumstances may result in an additional loss of protein<sup>32</sup> and a decrease in the osmotic pressure. Hemocentration is present in most instances of shock, and the greatest need is for plasma, rather than erythrocytes.<sup>33</sup> Plasma and serum present the additional advantage that compatibility tests are not necessary, and there is less delay in instituting treatment than if whole blood is used. Recent work indicates that serum presents certain advantages over plasma if a prolonged period of storage is contemplated.

As stated previously, diminution of the blood volume and vasoconstriction are prominent features of secondary shock. These alterations result in cold extremities. It should be remembered that there is not an equal reduction in blood flow throughout the body and that the extremities are cold, in part at least, because some of their circulation is diverted to more vital structures, such as the brain, heart, and adrenals. Further, it should be noted that the internal temperature may not be depressed, even when that of the extremities is low. It has been observed clinically that the condition of patients in shock may become

worse if intensive efforts are made to elevate the skin temperature. Mason and I<sup>34</sup> found recently that animals in shock as a result of hemorrhage or trauma survive longer with a depressed than with a significantly elevated skin temperature. It is not our impression that cold applications should be used in the treatment of patients in shock, but rather that the skin temperature should not be raised by applying hot water bottles and other heating devices unless the reduction of blood volume is relieved by the introduction of blood or plasma.

The use of inhalations of high concentrations of oxygen has been advocated in the treatment of shock. The results in treating traumatic shock have not been as encouraging in our hands as had been anticipated. This form of therapy is indicated particularly in the peripheral circulatory failure which accompanies pneumonia or intestinal distention.<sup>35</sup> A form of therapy upon which much work is being performed at present is the use of adrenal cortical extract. Active preparations have been available for only a few years, and it is difficult, as yet, to assess their value. In shock due mainly to the loss of sodium chloride and water, this form of therapy appears to be of value. It remains to be ascertained whether adrenal cortical extract and desoxycorticosterone acetate are of value in reducing the permeability of damaged capillaries. Many encouraging reports have appeared recently, and the results of further studies are awaited with interest.

In closing, I should like to repeat that the mechanism responsible for the development of some types of peripheral circulatory failure is fairly well understood but that information on other types is scanty. The available clinical and experimental evidence indicates that local loss of fluid is the most frequent initiating factor and that replacement of the escaped blood and fluid is usually the most effective therapeutic procedure. There are, however, many causes of shock, and attempts to explain all instances by one cause result only in confusion. One is not justified in assuming that all forms of shock are produced in the same way, and hence dogmatic statements regarding therapy may be in error. There are, therefore, many unanswered questions, and it is to be hoped that some future George E. Brown lecturer will be able to report a solution of many of the perplexing problems.

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## CARDIOLOGY AS A SPECIALTY

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THE study and treatment of heart disease and the identification of a normal heart are of great importance and wide interest, the prerogative of no individual, group, school, or country. Every doctor and, indeed, every layman is vitally concerned: the obstetrician with the fetal heart action, the pediatrician with the heart of the growing child, the internist with that of the adult, although he often leaves the last ages of man, that is, geriatrics, to the general practitioner, the surgeon with preparation for the strain of operation and aftercare, the military officer with the soldier's heart, and the family doctor and the layman with the entire period from birth to death. A varying degree and kind of knowledge is appropriate for each one of these. The pediatrician does not need to know much about the failing heart of coronary occlusion, with myocardial infarction; the internist and the military surgeon have little knowledge of the puzzling congenital heart problems of infancy; and the family doctor every so often encounters a rare or difficult case of heart disease for the elucidation of which he needs expert help in diagnosis and treatment. Man is not, however, just one age or one problem, any more than he is one organ, and so he must be viewed from every angle on the broad base of interest in him as a whole. It is in this respect that those who are not only interested but also trained in the study of the normal and abnormal heart of man from the cradle, in fact from the womb, to the grave, have a useful role to play, in fact, a role that cannot be, or at any rate has not been, played by any of the other medical workers I have mentioned. That is the role of the cardiologist.

Anyone may be interested in cardiology, may read intensively or extensively on the subject, may attend meetings such as this, or may do research on certain of its problems, but the practicing cardiologist, as such, must do more than this to be worthy of the name, as must obstetricians, surgeons, neurologists, and professors of internal medicine in their respective fields. He must first have a solid foundation, based on training and knowledge in cardiovascular anatomy and physiology. He must have a sound experience and knowledge of medicine in general, and of the vital interrelationships of all organs and systems in the body. He must have knowledge and experience in the judgment and handling

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of personalities, one of the most critical of all attributes of practicing physicians. He must continue to keep abreast of, and have an actual, although necessarily a minor, hand in following (not initiating, of course, except in rare instances) advances in other fields of medicine and surgery and of his profession as a whole. Most important of all, based essentially on all this, he must have had, and he must continue to have, rich, first-hand, constant experience in handling patients with heart troubles, real or imaginary. A general internist does not have time to do this, nor does the family doctor, for, following the old adage, they must learn "less and less about more and more" while the specialist learns "more and more about less and less."

Medicine has become a very extensive profession and requires many different general and special workers. Truly, one field is as important as any other field, whether general practice, teaching, laboratory work and research, administration, or specialization. All of these fields are fascinating to many medical students and young graduates, as they were to me, but one must make a choice, guided often, of course, by opportunity. One cannot now, as one could a generation ago, do everything. To illustrate this point I shall take the liberty of citing my own experience, for I know it best. While still an intern, I appreciated that it was impossible to do all of the things I should like to do in medicine. At first, I was very keen on obstetrics, and then on pediatrics. Later I thought I should like to be a practitioner or professor of general medicine, or a dean. Then came the opportunity, and, with it, the realization of the value of studying intensively in a special field, and so I selected cardiology with my eyes open, realizing that, if I wanted to become well grounded in that field, I could not spend so much time in the other fields. It was as plain as day and has continued to be so ever since. Patient perseverance during a good many years of preparation and of practice has brought me so much satisfaction and happiness that I am eternally grateful to the fates and for the advice I received in the beginning from those who steered me into this career and to those who have helped to keep me there, although I have been tempted frequently to do otherwise in this day and age of restless change. I am also grateful to those who have insisted that I must continue every year to have first-hand knowledge through hospital experience and responsibility in other fields of internal medicine.

I have stated my experience simply as an example of what I believe should be considered an essential for qualification as a special worker in the field of cardiovascular disease. Many of you here today are doubtless internists with a natural interest in heart disease, but without expectation or desire to concentrate primarily on cardiology. Some of you, however, are keen to do so, and to you I urge a program of the most careful grounding and intensive years of preparation, with your feet all the time firmly planted on the ground. We must recognize espe-

cially that electrocardiography, phonocardiography, and other tests of cardiovascular function, both normal and abnormal, are simply parts of the complete whole. To own an electrocardiograph and to perform tests of the rate and volume of the circulation are but small beginnings.

In closing, there is one other point I should like to mention, and that is the occasional remark one hears about the narrowness of specialists. Of course specialists may be narrow, but such a remark as a general observation is erroneous. Broad- or narrow-mindedness, philosophic points of view, and the value of the physician to his profession do not depend upon the particular kind of medical work that is being done; they depend upon the personality, training, industry, and environment of the individual. The family doctor may be broad- or narrow-minded, no matter how *extensive* his knowledge and experience may be; the specialist may be broad- or narrow-minded, no matter how *intensive* his knowledge and experience may be. It is of prime importance, therefore, for the specialist, as well as for the family doctor, to keep closely in touch with broad-minded associates in the field of medicine.

## THE EFFECT OF SEX HORMONES ON THE PRODUCTION OF ERGOTAMINE GANGRENE IN RATS

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THE observation of McGrath,<sup>1</sup> in 1935, that estrogenic hormone prevents the production of ergotamine gangrene in the tail of female, but not of male, albino rats aroused considerable interest. His results not only stimulated further experimental studies, but also served as a foundation for clinical trial<sup>2</sup> and the increasing use of sex hormones in the treatment of peripheral vascular diseases. In view of the similar anatomic changes in ergotamine gangrene and thromboangiitis obliterans and the rare incidence of the latter disease in women, the observation of McGrath gave rise to speculative considerations as to the importance of a hormonal factor in the etiology of thromboangiitis obliterans.

Suzmann, Freed, and Prag<sup>3</sup> and Ratschow and Klostermann<sup>4</sup> reported confirmatory evidence of McGrath's work. Both groups of investigators, however, extended their studies in different directions from the original studies of McGrath. Suzmann, Freed, and Prag stated that the administration of repeated doses (500 I.U.) of keto-hydroxy-estrone furnished the same degree of protection to castrated male rats as to normal female rats. Ratschow and Klostermann also reported observations on normal and castrated rats of both sexes, including, for the first time, studies on the effect of male sex hormone. Normal male rats were found to be protected by testosterone propionate, but not by estradiol benzoate. The reverse occurred in normal female rats, which were protected by estrogenic hormone, but not by testosterone. In castrated male rats, both female and male sex hormones (the latter to a somewhat lesser degree) prevented ergotamine gangrene. Female castrated rats showed a response only to estrogenic hormone; testosterone rather enhanced the severity of the gangrenous lesions. Further studies by Cobet, Ratschow, and Steckner<sup>5</sup> with synthetic substitutes for follicular hormone, called "diethylstilboestrol," indicated that these compounds did not show the sex-specific action of genuine female sex hormone; they furnished protection to normal female and male rats, and also to

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castrated animals of either sex which were subjected to ergotamine administration.

Loewe and Lenke,<sup>6</sup> however, in an attempt to confirm the results of McGrath, were unable, in the first place, to produce gangrene by a single injection of 50 to 100 mg. per kilogram of ergotamine tartrate with a sufficient degree of regularity to satisfy experimental criteria. This was the technique first used by Rothlin,<sup>7</sup> and later by McGrath. Having established a method which would consistently produce gangrene in 100 per cent of the animals by using a minimal dose of 50 mg. per kilogram of freshly prepared ergotamine tartrate solution, given in divided doses over a period of three days, Loewe and Lenke were unable to observe any protective action of estrogenic hormones as measured by incidence, extent, or rapidity of gangrene in normal female, male, and castrated male rats. They used an aqueous solution of theelin in daily injections of 2 to 10 rat units (dosage of McGrath), then 15 to 30 rat units, and, finally, 500 rat units daily of progynon-B in oil. Since a rat unit is considered to be from three to ten times as efficient as an international unit, the latter dosage exceeded that of Suzmann, Freed, and Prag (500 I.U.), and even that of Ratschow and Klostermann (1,000 I.U.).

Because of these contradictory results, further studies to clarify this problem seemed desirable. We were especially interested in the possible effect of testosterone, for no attempt had been made to repeat the experiments of Ratschow and Klostermann. The observation that testosterone was as effective in male rats as estrogen in females seemed of interest, not only experimentally, but also from the practical point of view. These observations also varied somewhat from certain inferences which might be drawn from the results of McGrath. The observation that estrogen prevents ergotamine gangrene was considered as suggestive evidence that female sex hormone might be responsible for the rare incidence of thromboangiitis obliterans in women. Following this line of reasoning, one might expect that testosterone would either remain ineffective or even facilitate the production of ergotamine gangrene.

While our experiments were in progress, Thomas<sup>8</sup> published his observations on the effect of female and male sex hormone on ergotamine gangrene. Using 20 I.U. of theelin daily, he was, like Lowe and Lenke, unable to confirm the results of former investigators. He also included one group of ten female and ten male rats which received testosterone propionate in daily injections of 0.5 mg. This likewise proved ineffective in preventing ergotamine gangrene. However, the dosage chosen by Thomas was only 0.1 of that used by Ratschow and Klostermann.

#### METHOD

Our experiments were carried out on 155 male and female albino rats of the Wistar strain. These animals were from 60 to 120 days old, and their average

weight was about 150 Gm.; litter mates were distributed evenly in the various groups. The rats which were given Purina dog chow\* and water ad lib. were controlled as to weight and normal general appearance for about a week before the experiment was started. Precautions were taken to provide for adequate simultaneous controls in each of five separate experiments.

The tail gangrene was produced by using a commercial preparation of ergotamine tartrate.† In preliminary experiments, both the single large injection used by McGrath and the repeated small injections employed by Ratschow and his collaborators were found to be unsatisfactory for albino rats of the Wistar and Okade strains. Larger single doses produced a high mortality from toxic effects, and daily injections of 0.5 mg., continued for weeks, failed to produce even the slightest changes in the tails of our rats. However, doses of 200 to 300 mg. per kilogram, when given in divided doses of 12.5 mg. per kilogram twice daily, at two-hour intervals, were found to produce gangrene in a large percentage of forty-one rats during preliminary experiments. This method of ergotamine administration was used in our experiments. The rats received two injections daily during a period of eight days, or for a shorter period of time if gangrene appeared earlier. The general toxic effects produced by the first injection of ergotamine tartrate developed within fifteen to sixty minutes and lasted for several hours, after which the animals gradually recovered. Subsequent doses were attended with a gradual decrease in the severity of these general toxic effects, i.e., tolerance seemed to develop. In addition to general weakness, apathy, and changed appearance of the fur, many animals exhibited other symptoms, such as diarrhea and hematuria. Rubor, cyanosis, and pallor at the end of the tail preceded the appearance of gangrene in most of the animals. In some rats, however, the initial changes disappeared and trophic changes, such as loss of hair at the tip of the tail, with localized atrophy of the skin, supervened.

Testosterone propionate,‡ in daily doses of 1.0 mg. and 10.0 mg., and estradiol benzoate, in a daily dose of 0.05 mg., which is equal to 500 I. U., were the preparations used in this study. The substances were administered subcutaneously in dilutions so adjusted that each dose was dissolved in 0.2 to 0.4 c.c. of sesame oil. The control rats were given equivalent doses of plain sesame oil. In some experiments a second group of controls which were receiving no injections other than ergotamine was included. The injections were given daily for seven to ten days before, during, and for seven to ten days after, the period of ergotamine administration.

## RESULTS

The results of five separate experiments are shown in Table I.

In Experiment I, gangrene was produced in seven of nine male control rats which were receiving ergotamine according to the technique above described. The administration of 10 mg. of testosterone propionate daily did not prevent the production of gangrene in the male rats of the experimental group; the average extent of the gangrene of the tail was even greater than in the control group. The occurrence of gangrene was 77 per cent for both controls and treated animals.

\*Product of the Ralston Purina Co., St. Louis, containing a mixture of grains and alfalfa hay, supplemented by vitamins and minerals.

†The ergotamine tartrate solution (gynergen) was supplied through the courtesy of Dr. Durward Jones, Sandoz Chemical Works, Inc., New York, N. Y.

‡The hormone preparations were supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J.

Experiment II also includes observations on the effect of testosterone on female rats. In this instance, only 1 mg. of testosterone propionate was given daily to six male rats, of which only one developed gangrene only 0.3 cm. in extent; the incidence of gangrene was lowered to 15 per cent. The control group, however, showed a decrease of 40 per cent, for only two of five animals were found to have gangrenous lesions of very slight degree. Upon repeating this experiment with twelve animals in the control and experimental groups (Experiment III), we found that the incidence and extent of gangrene were rather higher in the rats which received testosterone. Female rats treated with different amounts of testosterone (Experiment II) presented no significant difference from controls with respect to the occurrence or degree of gangrenous lesions produced by ergotamine.

TABLE I

| EXPERIMENT NO. | DATE       | SEX | INJECTION  |            | TOTAL NO. OF RATS | GANGRENE    |    |                  |                        |
|----------------|------------|-----|------------|------------|-------------------|-------------|----|------------------|------------------------|
|                |            |     | SUBSTANCE  | DAILY DOSE |                   | NO. OF RATS | %  | AV. EXTENT (CM.) | AV. DAY OF APPEARANCE* |
| I              | Dec., 1939 | M   | Sesame oil | 0.4 c.c.   | 9                 | 7           | 77 | 0.9              | 8                      |
|                |            | M   | Test. p.   | 10 mg.     | 9                 | 7           | 77 | 1.6              | 7                      |
| II             | Jan., 1940 | M   | Sesame oil | 0.4 c.c.   | 5                 | 2           | 40 | 0.3              | 13                     |
|                |            | M   | Test. p.   | 1 mg.      | 6                 | 1           | 15 | 0.3              | 17                     |
|                |            | F   | Sesame oil | 0.4 c.c.   | 12                | 5           | 42 | 1.2              | 10                     |
|                |            | F   | Test. p.   | 10 mg.     | 5                 | 2           | 40 | 1.1              | 9                      |
|                |            | F   | Test. p.   | 1 mg.      | 6                 | 3           | 50 | 0.7              | 12                     |
|                |            | F   | Test. p.   | 1 mg.      | 6                 | 3           | 50 | 0.7              | 12                     |
| III            | Feb.       | M   | Sesame oil | 0.4 c.c.   | 12                | 8           | 67 | 1.2              | 14                     |
|                |            | M   | Test. p.   | 1 mg.      | 11                | 8           | 73 | 1.9              | 9                      |
| IV             | March      | M   | None       |            | 3                 | 1           | 33 | 0.2              | 10                     |
|                |            | M   | Sesame oil | 0.4 c.c.   | 10                | 6           | 60 | 0.5              | 11                     |
|                |            | M   | Estr. b.   | 0.05 mg.   | 10                | 2           | 20 | 0.3              | 14                     |
|                |            | F   | None       |            | 3                 | 0           | 0  |                  |                        |
|                |            | F   | Sesame oil | 0.4 c.c.   | 10                | 0           | 0  |                  |                        |
|                |            | F   | Estr. b.   | 0.05 mg.   | 9                 | 0           | 0  |                  |                        |
| V              | May        | M   | Sesame oil | 0.4 c.c.   | 10                | 6           | 60 | 0.9              | 11                     |
|                |            | M   | Estr. b.   | 0.05 mg.   | 9                 | 7           | 77 | 0.5              | 9                      |
|                |            | F   | Sesame oil | 0.4 c.c.   | 9                 | 7           | 77 | 1.1              | 7                      |
|                |            | F   | Estr. b.   | 0.05 mg.   | 7                 | 6           | 85 | 1.0              | 12                     |

\*Days after the initiation of ergotamine injections.

Test. p., Testosterone propionate; Estr. b., estradiol benzoate.

Having observed no protective effect of male sex hormone against ergotamine gangrene in male and female albino rats, we proceeded to study the effect of estrogenic hormone. In Experiment IV, ten female rats which received estradiol benzoate (0.05 mg. daily) were found to be free from gangrenous lesions, but thirteen female control rats also showed absence of gangrene. Male animals treated with the same daily dose of estrogenic hormone also exhibited a low incidence of gangrene. Only two of ten animals were affected, whereas the control group showed a higher percentage. In repeating the experiment (Experiment V), we found that male and female rats which received estrogen showed a higher incidence of gangrene than their respective group of controls.



There was, furthermore, no evidence that the general toxic effects produced by ergotamine tartrate were less pronounced in those rats which received male or female sex hormones. As a matter of fact, the highest number of deaths was recorded in a group of female rats which received estrogenic hormone.

#### COMMENTS

From the results of these experiments it becomes apparent that, provided adequate precautionary measures, including simultaneous controls and duplication of each experiment, are carried out, neither testosterone propionate nor estradiol benzoate exerts any effect on the incidence, extent, or rapidity of gangrene produced by ergotamine tartrate in the tail of adult male and female albino rats.

Marked variations in the incidence of gangrene occur in the control as well as the treated groups, which is evidence of the unreliability of the ergotamine method. Previous studies, in which a so-called "gangrenous dose" was determined by preliminary assays, so that the carrying out of simultaneous controls with each experiment was not deemed necessary, are certainly open to criticism. There is no doubt that this explains some of the more capricious conclusions.

A definite explanation cannot be offered for the variation in the dose of ergotamine tartrate required for the production of gangrene by the various investigators. It seems probable that preparations of different potencies must have been used. Variations in susceptibility to ergotamine poisoning between different strains of rats must be considered as a possibility. We obtained similar results, however, in two different strains of rats which were used in preliminary experiments. Perhaps inadequate nutrition might also account for differences in susceptibility. The rats in this study showed a rather high resistance against the ergotamine tartrate which we used. When considered in terms of a 70-kg. man, the daily dose of ergotamine tartrate required to produce gangrene would amount to 1,750 mg. This is of interest in regard to the increasing clinical use of ergotamine tartrate in the treatment of migraine, pruritus, and disturbances of the sympathetic nervous system.

Since the factors of strain, age of rats, nutrition, dosage, and technique of administration of ergotamine tartrate were not variable beyond narrow limits in our experiments, the differences in the incidence of gangrene in the control groups remain unexplained. The unreliability of the ergotamine method was also noted by Loewe and Lenke when a commercial preparation was used. Unfortunately, we were not able to obtain dry ergotamine powder, such as was used by these investigators to prepare fresh ergotamine tartrate solution on the day of the experiment. There are, however, indications that other factors which were variable in the successive experiments, such as surrounding temperature or seasonal influences, might be responsible for these variations.

Griffith and Comroe<sup>9</sup> presented experimental and clinical evidence that hyperthyroidism and peripheral vasodilatation are factors which facilitate the production of ergotamine gangrene. The stimulating effect of prolonged exposure to cold on the thyroid glands of rats is known through the work of Cramer,<sup>10</sup> and also of Starr and Roskelly.<sup>11</sup> On the other hand, peripheral vasodilatation produced in the tails of rats by a high surrounding temperature might perhaps also predispose to gangrene of the tail after ergotamine poisoning. Observations in this laboratory have shown that the skin temperature of the tails of rats very closely follows variations of the room temperature. Thus, it appears not unlikely that external factors, such as low and high surrounding temperatures, influence the tolerance of rats to ergotamine tartrate. Further studies on the influence of similar external factors on the production of ergotamine gangrene are suggested.

#### CONCLUSIONS

The administration of testosterone propionate or estradiol benzoate does not exert any influence on the incidence, extent, or rapidity of the gangrene produced by ergotamine tartrate in the tails of adult male and female albino rats.

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## RHEUMATIC CARDITIS IN A TROPICAL COUNTRY

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THE epidemiology of rheumatic fever has been well covered,<sup>1-3</sup> but we wish to point out the influence of climatic conditions. The following data may prove useful for future reference.

Costa Rica is situated in Central America, and its capital, San José, lies more or less at 10° latitude North. This town occupies a healthy position on a narrow plateau, 25 miles long by 12 miles wide, whose altitude above sea level varies between 3,000 and 4,000 feet. The characteristic features of a tropical climate, somewhat influenced by the altitude, are present. The average humidity is 80 per cent, and the temperature is 19° C. (66° F.), with extremes ranging from 12° C. (54° F.) to 32° C. (90° F.). The average daily precipitation during the rainy months is 10 mm., that is, from June through November. The dry season ("verano") starts in December; it is influenced by northeast winds which bring dry and fresh weather. The average barometric pressure is 66.5 mm., with minimum oscillations. The sun shines most of the time.

In various towns around San José, rheumatic fever and chorea are known to be present, although the exact incidence cannot be ascertained at present because of lack of information from hospitals and various government agencies which we have consulted. In the period from April, 1936, to April, 1939, we found twenty-two cases of rheumatic fever, chorea, and endocarditis among 3,771 clinical records from the pediatric ward of the Hospital San Juan de Dios, at San José.<sup>4</sup> The diagnoses were made by different observers and were not checked by us. The diagnostic criteria of heart involvement were unsatisfactory, for no electrocardiograms were taken, and therefore it is possible that other cases escaped unnoticed. The incidence of mitral stenosis in the last 1,000 autopsies performed at the same hospital was 1.1 per cent (from April, 1939, to May, 1941). This figure is higher than the one given by Harrison and Levine<sup>3</sup> at the Charity Hospital in New Orleans.

This report covers some cases which were analyzed by clinical and laboratory methods (roentgenology, electrocardiography, sedimentation rate, etc.). They come from our own private practice in the last three years, but other cases in which we are unable to present the electrocardiographic record are omitted, including one patient who died with typical subacute bacterial endocarditis, superimposed on rheumatic lesions (Table I).

## COMMENT

Various reports<sup>1-3</sup> have shown that rheumatic fever and carditis seem to be more common in the northern part of the United States than in its southern regions. Therefore, it has been concluded that, in order to prevent recurrences, rheumatic patients should go south. But what

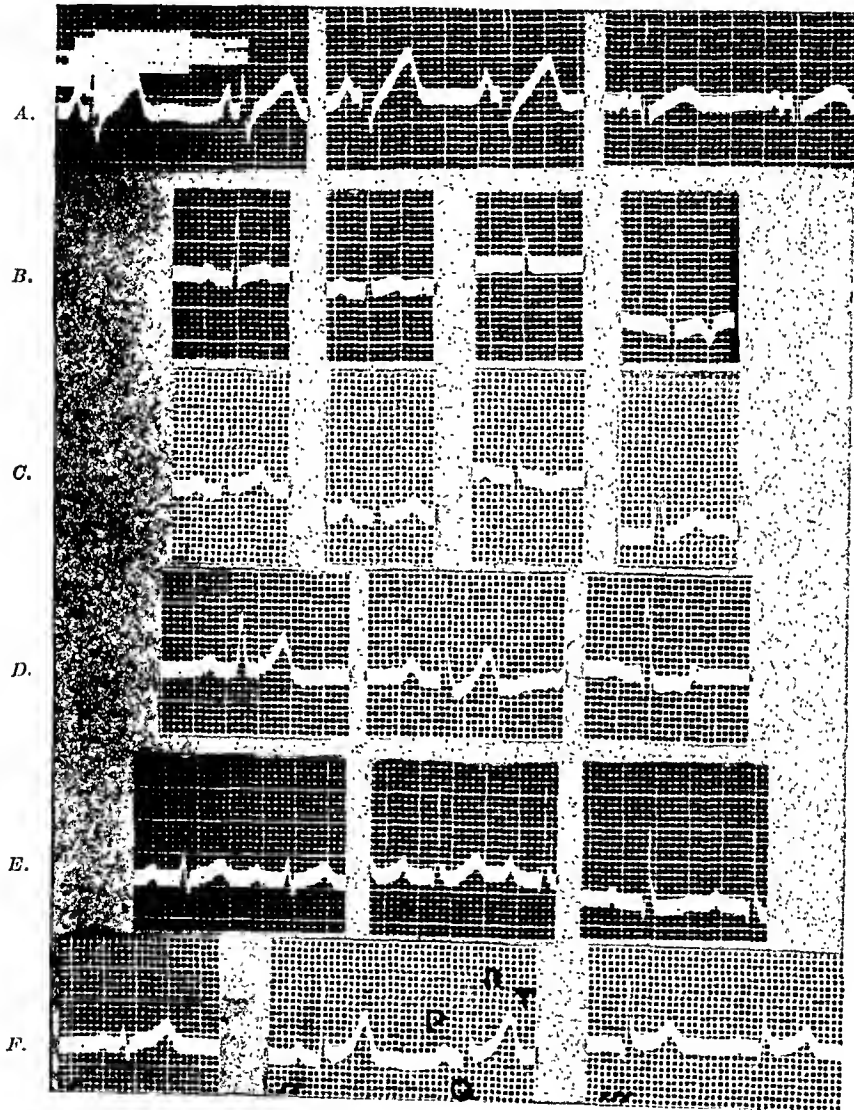


Fig. 1.

has been disregarded by most observers is the fact that, although this malady may occur less frequently, it has by no means been proved that it is less serious or that its course is not the same or at least delayed. Here we have cases occurring in a tropical climate, and, in the course of a few years, the patients develop multiple valvular lesions and die.

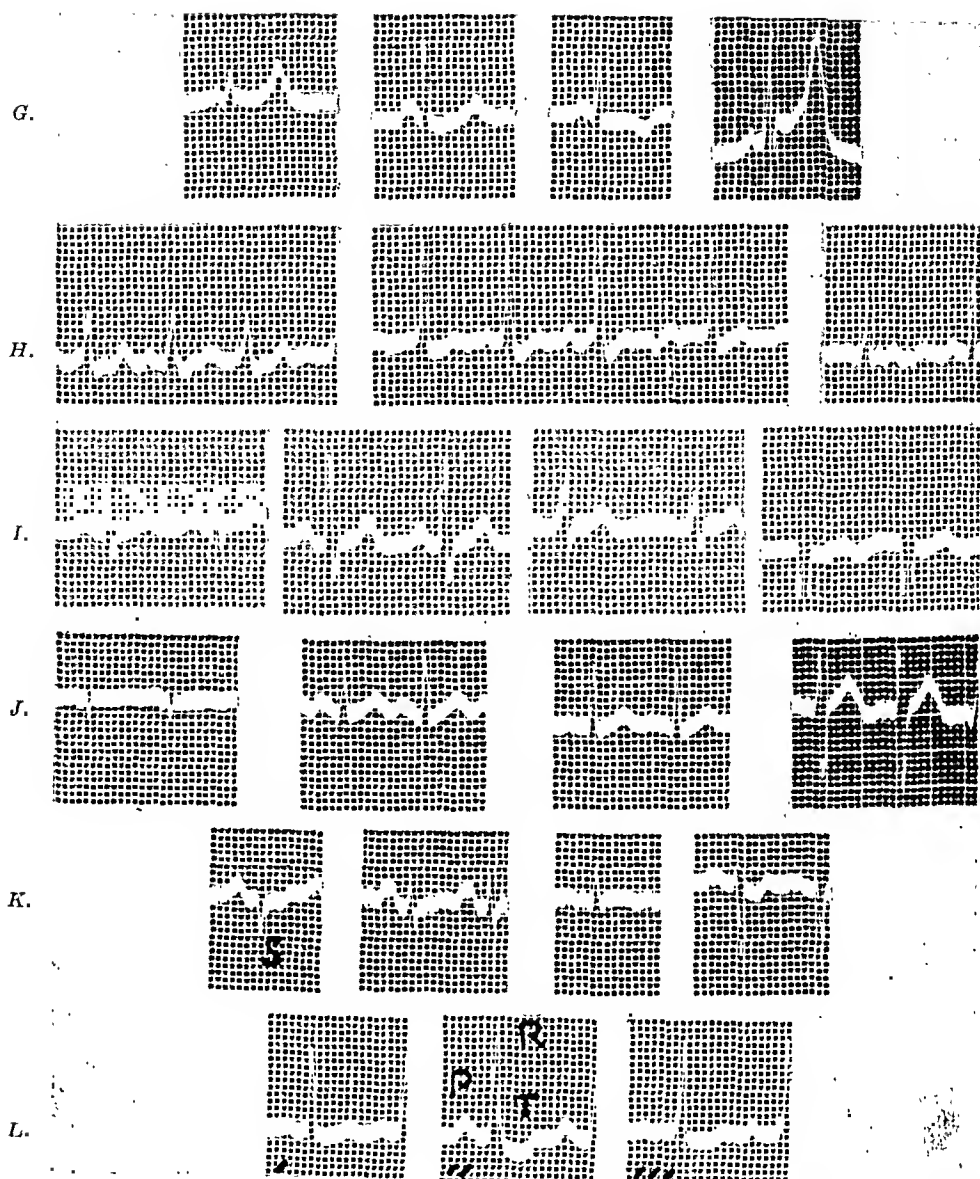


Fig. 2.



Fig. 3.—Electrocardiogram of a man, 18 years old, who died three years after the onset of rheumatic heart disease. It shows auricular fibrillation, complete A-V block, and left ventricular premature beats (bigeminy). Digitalis effect on RS-T segment; extreme R. V. preponderance.

In the study made by Jones and his associates,<sup>5</sup> caution has already been expressed with regard to the advisability of transportation to a sub-tropical climate.

It is evident that many factors may be concerned with the occurrence of the rheumatic infection in a given child or adolescent, but climate alone should not be given undue importance; other factors also play a role in determining the evolution and cardiac sequelae.

TABLE I

| AGE<br>(YEARS) | SEX | CHRONOLOGICAL DEVELOPMENT<br>OF THE DISEASE   | ELECTROCARDIOGRAM  |
|----------------|-----|---|--|
| 11             | M   | 1938, rheumatic fever and chorea<br>1941, mitral valve disease  | Fig. 1A, high amplitude of P waves (2.5 mm.)   |
| 22             | M   | 1939, acute rheumatic pericarditis<br>1941, slight "rouff-ta-ta"  | Fig. 1B, May, 1939<br>Fig. 1C, July, 1939<br>Fig. 1D, March, 1941, changing amplitude of P-R and T waves   |
| 17             | M   | 1940, rheumatic fever and pericarditis<br>1941, no symptoms or signs  | Fig. 1E, August, 1940<br>Fig. 1F, October, 1940, changing amplitude of waves and P-R segment (0.21-0.18)   |
| 31             | M   | 1940, early (?) mitral valve disease  | Fig. 2G, short P-R, notched P, and very high T <sub>1</sub> (15 mm.)                                       |
| 36             | M   | 1911, chorea<br>1941, mitral and aortic valve disease   | Fig. 2H, auricular fibrillation  |
| 14             | M   | 1937, rheumatic fever<br>1941, mitral valve disease   | Fig. 2I, notched P, measuring 0.10 sec.; notched R <sub>2</sub>  |
| 10             | F   | 1939, undetermined fever<br>1941, mitral and aortic valve disease; unknown cause of death                         | Fig. 2J, notched P, measuring 0.12 sec.; flat T <sub>1</sub> ; definite R.V. preponderance                 |
| 25             | F   | 1923, 1934, 1938, rheumatic fever<br>1941, mitral and aortic valve disease; unknown cause of death                | Fig. 2K, plateau P <sub>2</sub> ; diphasic or isoelectric T; tendency to low R; extreme R.V. preponderance |
| 30             | F   | 1924, rheumatic fever<br>1940, mitral and aortic valve disease<br>1941, acute, fatal serosanguineous pericarditis | Fig. 2L, notched P <sub>2</sub> , measuring 0.12 sec.; digitalis effect on RS-T segment                    |
| 18             | M   | 1936, "palpitations"<br>1938, rheumatic panvalvulitis<br>1939, fatal congestive heart failure                     | See Fig. 3   |

## SUMMARY

We have tried to show that living in a tropical country by no means constitutes a safeguard against rheumatic infection or the development of severe rheumatic carditis. We present data from our own practice and from the Hospital San Juan de Dios.

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## THE PERIPHERAL BLOOD FLOW IN MYXEDEMA AS COMPARED WITH THAT IN HYPERTHYROIDISM

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THE cardiac output,<sup>1</sup> the circulating blood volume,<sup>2</sup> the velocity of blood flow, the pulse rate, the pulse pressure, and the vital capacity<sup>3</sup> are decreased when the basal metabolism<sup>4</sup> is low in myxedema. The pale, cold, dry skin of patients suffering from this disease suggested that there might be alterations of peripheral blood flow. Objective measurements, however, are not in the literature relating to the amount of blood allocated to the periphery. Stewart and Evans<sup>5</sup> found that the peripheral blood flow in hyperthyroidism was increased and that it decreased with the administration of iodine and further still after subtotal thyroidectomy, so that there was a linear relationship between basal metabolic rate and peripheral blood flow. In these patients the increase in peripheral blood flow accounted for the pink, moist skin which they exhibited. It was of interest, therefore, to measure the peripheral blood flow in myxedema, which is at the other end of the metabolic scale from hyperthyroidism. These data have now been accumulated and compared with measurements on patients with hyperthyroidism.<sup>5</sup>

Six women suffering from myxedema were observed. Four of them suffered from spontaneous myxedema (E. S., L. C., M. P., and R. M., Table I) and two, from postoperative myxedema (M. K., and E. B., Table I). Data on six female hyperthyroid patients (C. DiP., M. H., E. B., K. H., N. L., and A. S.), on whom measurements of peripheral blood flow had been made at the same environmental temperatures which prevailed at the time the myxedema patients were observed, were chosen for comparison (Table II).<sup>5</sup> All subjects in both groups had normal sinus mechanism and no signs or symptoms of congestive heart failure.

### METHODS

Measurements of peripheral blood flow were made with techniques similar to those used in other studies of the peripheral blood flow by Stewart and Jaek<sup>6</sup> and Stewart and Evans.<sup>5</sup> In order to use this method, certain data were required, namely, recordings of skin temperature, for which a Hardy radiometer was used,

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of rectal temperature, of oxygen consumption, of height, and of body weight. In addition, the blood pressure, the pulse rate, and the arm-to-tongue circulation time (decholin<sup>7</sup>) were recorded.

#### PLAN OF OBSERVATIONS

The order in which data were recorded was the same as that used in the observations on the patients with hyperthyroidism.<sup>5</sup> Six sets of skin and rectal temperatures, made at twenty-minute intervals, appeared to be sufficient. From these recordings, five average periods of peripheral blood flow were calculated.<sup>5</sup> The blood pressures and pulse rates were recorded during free intervals between temperature readings. The arm-to-tongue circulation time was measured after the last estimate of oxygen consumption. Observations subsequent to the initial phase were made in exactly the same sequence on each patient, and care was taken to reproduce the same environmental temperature.<sup>5</sup> Observations were made before treatment was instituted, and again on several occasions after the administration of thyroid extract, until the basal metabolic rate approached normal.

#### RESULTS

*Metabolic Rate and Peripheral Blood Flow.*—Before treatment, when the basal metabolic rate was low, the peripheral blood flow was also decreased. With progressive elevation of the basal metabolic rate to normal during the administration of thyroid extract, successive increases in peripheral blood flow occurred (Tables I and II) (Fig. 1).

*Skin Temperature.*—The average skin temperature was decreased at first and increased with the administration of thyroid extract. The average temperature of the hands and feet showed similar trends for the whole group (Tables I and II).

*Rectal Temperature.*—Changes in rectal temperature did not follow any pattern (Tables I and II).

*Pulse Rate and Pulse Pressure.*—The pulse rates of each of the six patients and in the group averages showed trends parallel with changes in basal metabolic rate and peripheral blood flow, that is to say, they increased with the giving of thyroid extract. The average pulse pressure also rose, except in one patient (E. B.) (Tables I and II).

*Circulation Time.*—The circulation time was prolonged before treatment. It became shorter during treatment with thyroid extract (Tables I and II) (Fig. 1).

#### DISCUSSION

These observations show that, at a time when the basal metabolic rate was low in the myxedematous subjects, the peripheral blood flow was also decreased. During the progressive rise in basal metabolic rate with the administration of thyroid extract there were successive and parallel increases in peripheral blood flow (Tables I and II) (Fig. 1). This relationship between peripheral blood flow and basal metabolic rate was linear (Fig. 2). On the other hand, Stewart and Evans<sup>5</sup> found that, during thyrotoxicosis, when the basal metabolic rate was

TABLE I

DATA RELATING TO SIX PATIENTS WITH MIXEDEMA

| HIS-<br>TORY<br>NO. | NAME  | AGE<br>(YR.) | SEX | DIAG-<br>NOSIS                      | DATE                                     | HEIGHT<br>(CM.)                  | WEIGHT<br>(KG.)              | TOTAL<br>SUR-<br>FACE<br>AREA<br>(SQ.M.) | TOTAL<br>HEAT<br>PRODUC-<br>TION*<br>(CAL./<br>HR.) | AV.<br>ROOM<br>TEMP.<br>(° C.) | AV.<br>REC-<br>TAL<br>TEMP.<br>(° C.) | AV.<br>SKIN<br>TEMP.†<br>(° C.)  | AV.<br>HAND<br>TEMP.<br>(° C.) | AV.<br>FOOT<br>TEMP.<br>(° C.) | BASAL<br>META-<br>BOLIC<br>RATE<br>(%) | PE-<br>RIPI-<br>ERAL<br>BLOOD<br>FLOW<br>(C.C./<br>M <sup>2</sup> /<br>MIN.) | CIR-<br>CULA-<br>TION<br>TIME<br>(DE-<br>CHO-<br>LIN<br>(SEC.)) | PULSE<br>RATE<br>(PER<br>MIN.) | PULSE<br>PRES-<br>SURE<br>(MM.<br>HG) | THY-<br>ROID<br>EX-<br>TRACT<br>THER-<br>APY<br>(GM.<br>DAILY) |
|---------------------|-------|--------------|-----|-------------------------------------|--|----------------------------------|------------------------------|--|---|--------------------------------|---------------------------------------|----------------------------------|--------------------------------|--------------------------------|--|--|---|--------------------------------|---------------------------------------|--|
| 256220              | L. C. | 60           | F   | Sponta-<br>neous<br>myx-<br>edema   | 2/ 6/40<br>3/ 2/40<br>3/30/40<br>1/10/41 | 155.5<br>155.5<br>155.5<br>155.5 | 73.0<br>76.5<br>71.8<br>71.7 | 1.78<br>1.77<br>1.72<br>1.72             | 41.2<br>47.1<br>65.2<br>52.6                        | 27.6<br>27.5<br>27.7<br>27.5   | 36.79<br>36.96<br>37.46<br>36.82      | 33.76<br>33.78<br>34.4<br>34.17  | 33.2<br>34.3<br>34.4<br>34.2   | 32.2<br>33.8<br>35.1<br>33.8   | -30<br>-18<br>+16<br>-4                | 14<br>49<br>137<br>91  | 14.9<br>12.8<br>11.5<br>11.2                                    | 60<br>73<br>90<br>74           | 22<br>34<br>30<br>54                  | None<br>0.012<br>0.060<br>0.075                                |
| 258799              | E. S. | 32           | F   | Sponta-<br>neous<br>myx-<br>edema   | 2/13/40<br>4/ 5/40<br>5/14/40<br>1/13/41 | 167.5<br>167.5<br>167.5<br>167.5 | 63.1<br>63.4<br>61.7<br>59.4 | 1.71<br>1.71<br>1.70<br>1.69             | 40.1<br>43.4<br>48.6<br>62.5                        | 25.6<br>25.8<br>26.1<br>25.9   | 37.31<br>37.19<br>37.41<br>36.74      | 33.10<br>33.89<br>33.83<br>32.72 | 32.3<br>34.6<br>35.1<br>32.7   | 26.9<br>31.6<br>32.6<br>28.0   | -34<br>-29<br>-19<br>+5                | 22<br>61<br>71<br>92   | 21.8<br>20.1<br>12.5<br>10.9                                    | 49<br>48<br>59<br>60           | 20<br>30<br>36<br>34                  | None<br>0.045<br>0.120<br>0.210                                |
| 145380              | M. P. | 30           | F   | Sponta-<br>neous<br>myx-<br>edema   | 1/ 6/41<br>3/29/41<br>4/19/41            | 170.0<br>170.0<br>170.0          | 63.4<br>61.1<br>60.8         | 1.74<br>1.72<br>1.71                     | 49.8<br>58.8<br>60.0                                | 26.0<br>26.2<br>26.0           | 36.91<br>36.92<br>36.56               | 33.24<br>33.80<br>33.18          | 28.8<br>29.8<br>32.9           | 31.4<br>32.5<br>33.1           | -20<br>-6<br>-2                        | 10<br>78<br>79   | 12.9<br>12.2<br>12.3  | 60<br>68<br>64                 | 24<br>36<br>32                        | None<br>0.060<br>0.120   |
| 271344              | R. M. | 30           | F   | Sponta-<br>neous<br>myx-<br>edema   | 11/ 7/40<br>1/11/41<br>4/26/41           | 161.5<br>161.5<br>161.5          | 85.8<br>84.1<br>85.1         | 1.91<br>1.88<br>1.89                     | 50.8<br>58.6<br>67.6                                | 25.0<br>25.2<br>25.1           | 36.86<br>36.74<br>37.23               | 31.74<br>33.12<br>33.58          | 31.7<br>33.5<br>33.2           | 27.5<br>32.2<br>32.6           | -26<br>-13<br>0                        | 7<br>55<br>90  | 19.6<br>16.6<br>15.0  | 60<br>64<br>64                 | 12<br>26<br>24                        | 0.015<br>0.030<br>0.120  |
| 196749              | M. K. | 39           | F   | Postop-<br>erative<br>myx-<br>edema | 11/ 6/40<br>1/ 2/41<br>2/14/41           | 147.0<br>147.0<br>147.0          | 66.8<br>66.7<br>68.3         | 1.60<br>1.60<br>1.61                     | 32.8<br>53.4<br>58.6                                | 25.2<br>25.5<br>25.1           | 36.87<br>37.34<br>36.86               | 32.19<br>34.14<br>33.97          | 31.1<br>34.4<br>34.0           | 27.2<br>29.8<br>30.3           | -43<br>-7<br>+2                        | 33<br>68<br>87   | 17.0<br>14.9<br>12.4  | 60<br>66<br>64                 | 20<br>30<br>30                        | None<br>0.030<br>0.150   |
| 170489              | E. B. | 42           | F   | Postop-<br>erative<br>myx-<br>edema | 1/16/41<br>2/ 3/41<br>3/ 4/41            | 172.0<br>172.0<br>172.0          | 67.4<br>67.0<br>67.5         | 1.82<br>1.83<br>1.83                     | 43.7<br>62.7<br>68.0                                | 25.0<br>25.2<br>25.3           | 36.90<br>37.25<br>37.28               | 32.96<br>34.21<br>34.29          | 31.2<br>35.2<br>34.2           | 23.5<br>26.4<br>31.9           | -33<br>-7<br>-3                        | 9<br>71<br>81  | 19.5<br>15.1<br>14.0  | 68<br>72<br>68                 | 66<br>50<br>46                        | None<br>0.060<br>0.150   |

\*Calculated from oxygen consumption.<sup>5</sup>†Calculated from weighing the eleven individual skin temperatures according to the surface area represented by each.<sup>5</sup>

high the peripheral blood flow was increased. Parallel decreases in basal metabolic rate and peripheral blood flow occurred during iodine therapy, and both returned to normal levels after subtotal thyroidectomy (Table II).<sup>5</sup> The linear relationship between basal metabolic rate and peripheral blood flow in these two diseases is shown when data on all patients are plotted on the same chart (Fig. 2). With progressive increases from the low basal metabolic level of the myxedematous state to the high basal metabolic level of the hyperthyroid subjects, there was a progressive increase in the peripheral blood flow. The intercepts with the zero line were, however, slightly different (Fig. 2). The scattering of peripheral blood flow at various levels for individual patients was interpreted as due, in part, to different basal metabolic rates, and, in part, to different room temperatures for each patient (Fig. 1). Hick, Keeton, Glickman, and Wall<sup>8</sup> and Hardy and Soderstrom<sup>9</sup> have shown that there is a correlation between rise in environmental temperature and increase in peripheral blood flow. Observations published recently by Stewart and Evans<sup>5</sup> are in agreement with these findings. For this reason, care was exercised to keep environmental temperature approximately the same during all observations on any one patient.

TABLE II

AVERAGES OF MEASUREMENTS ON SIX PATIENTS WITH HYPERTHYROIDISM  
FOR COMPARISON WITH THOSE ON SIX PATIENTS  
SUFFERING FROM MYXEDEMA

|                        | BASAL<br>META-<br>BOLIC<br>RATE<br>(%) | PE-<br>RIPH-<br>ERAL<br>BLOOD<br>FLOW<br>(C.C./<br>M <sup>2</sup> /<br>MIN.) | CIR-<br>CULA-<br>TION<br>TIME<br>(SEC.) | PULSE<br>PRES-<br>SURE<br>(MM.<br>HG) | PULSE<br>RATE<br>(PER<br>MIN.) | AV.<br>SKIN<br>TEMP.<br>(° C.) | REC-<br>TAL<br>TEMP.<br>(° C.) | HAND<br>TEMP.<br>(° C.) | FOOT<br>TEMP.<br>(° C.) |
|------------------------|--|--|---|---------------------------------------|--------------------------------|--------------------------------|--------------------------------|-------------------------|-------------------------|
| <i>Hyperthyroidism</i> |  |  |   |                                       |                                |                                |                                |                         |                         |
| Before iodine          | +45                                    | 210  | 8.4                                     | 55                                    | 106                            | 34.63                          | 37.28                          | 35.2                    | 33.0                    |
| During iodine          | +24                                    | 139  | 10.6                                    | 45                                    | 80                             | 34.39                          | 37.19                          | 34.9                    | 31.8                    |
| After operation        | + 8                                    | 68   | 13.6                                    | 39                                    | 72                             | 33.66                          | 37.21                          | 34.6                    | 29.9                    |
| <i>Myxedema</i>        |  |  |   |                                       |                                |                                |                                |                         |                         |
| Before treatment       | -29                                    | 16   | 17.6                                    | 27                                    | 60                             | 32.83                          | 36.94                          | 31.4                    | 28.1                    |
| During thyroid extract | -12                                    | 65   | 14.1                                    | 35                                    | 69                             | 33.81                          | 37.10                          | 33.7                    | 31.2                    |
| During thyroid extract | - 2                                    | 87   | 12.6                                    | 37                                    | 66                             | 33.65                          | 36.92                          | 33.5                    | 33.3                    |

Before treatment, when the basal metabolic rate and peripheral blood flow were low, the average skin temperature was also decreased. Increases in average skin temperature occurred during the administration of thyroid extract.

In the subjects with hyperthyroidism, on the other hand, there was an elevation of average skin temperature before treatment, with a progressive decrease to normal levels during iodine therapy and after operation. In short, treatment of the myxedematous patients with

thyroid extract raised average skin temperature to normal levels, and iodine therapy and subtotal thyroidectomy in the case of the thyrotoxic patients decreased it to normal levels (Table II).

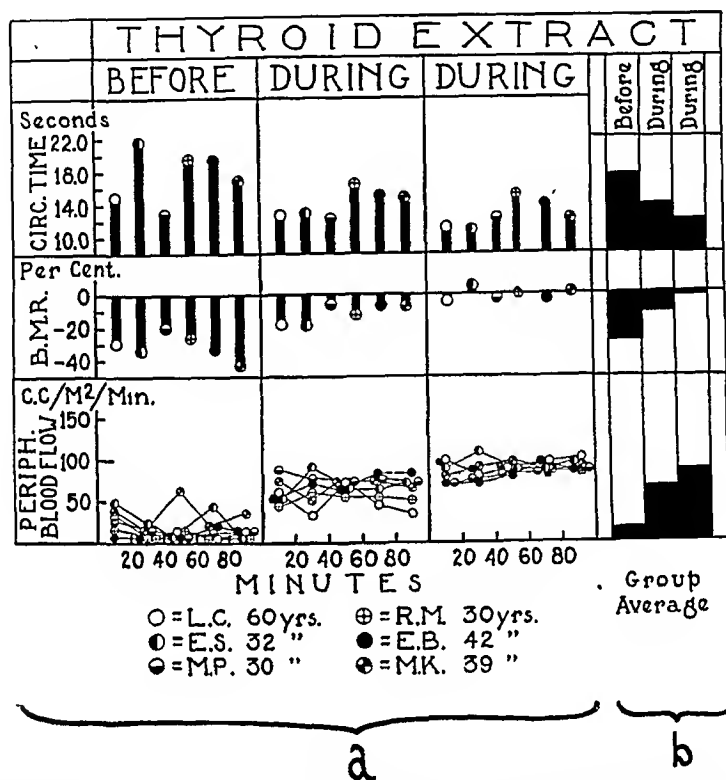


Fig. 1.—Peripheral blood flow, basal metabolic rate, and circulation time of six patients suffering from myxedema, before and during the administration of thyroid extract (Fig. 1a). Each patient is represented by a symbol. In Fig. 1b, averages for the data on the six patients are shown.

The recent studies on hyperthyroidism<sup>5</sup> showed no direct relationship between the temperature of the hands and feet and average skin temperature. This was the case also in myxedematous patients. In myxedema the average temperature of the hands followed average skin temperature more closely, whereas the average temperature of the feet more nearly paralleled the changes in peripheral blood flow and basal metabolic rate. The data on L. C. (Table I) (Fig. 3) are presented in detail to bring out these points.

The change in rectal temperature in each case, as well as the average rectal temperature of all patients in the myxedema group and in the hyperthyroid group, was much less marked than the alteration in average skin temperature (Tables I and II).<sup>5</sup> This emphasizes a point brought out by Burton,<sup>10</sup> namely, that, although rectal temperature has the larger weighting coefficient, surface (average skin) temperature is the more important because it changes more in short periods.

Stewart, Deitrick, and Crane<sup>1</sup> found that the cardiac output was low in myxedema and increased to normal with the rise in basal metabolic

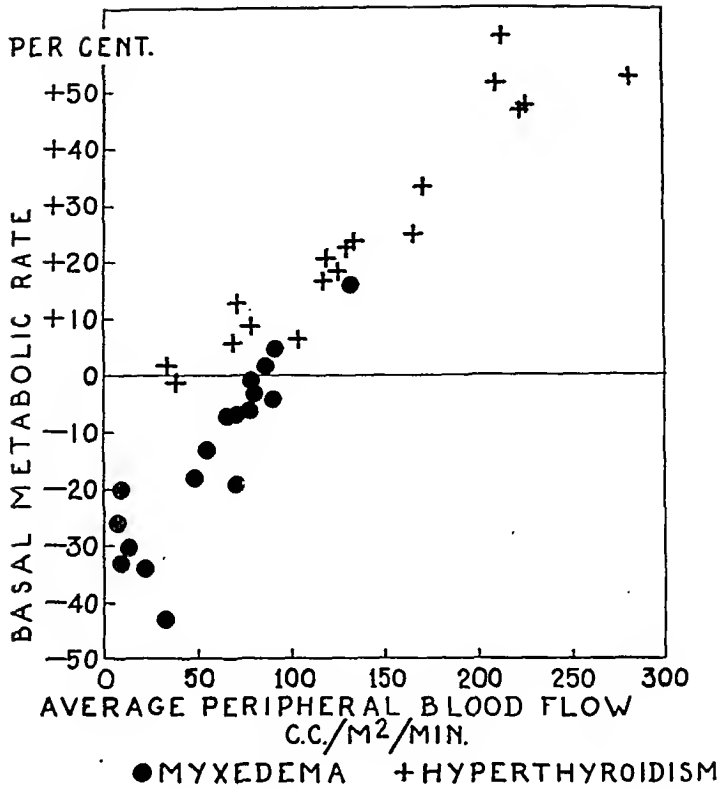


Fig. 2.—The data for the peripheral blood flow of the myxedema patients (Table 1) (Fig. 1) and of six hyperthyroid patients (Stewart and Evans<sup>5</sup>) are plotted against corresponding basal metabolic rates. A linear relationship is established, for, with the increase in basal metabolic rate from the low level of myxedema to the high level of thyrotoxicosis, the peripheral blood flow also increased.

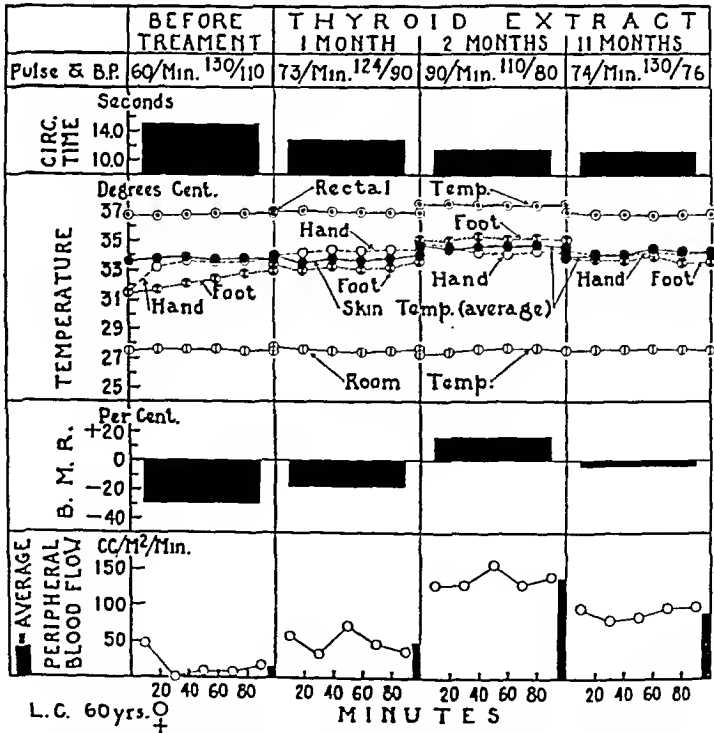
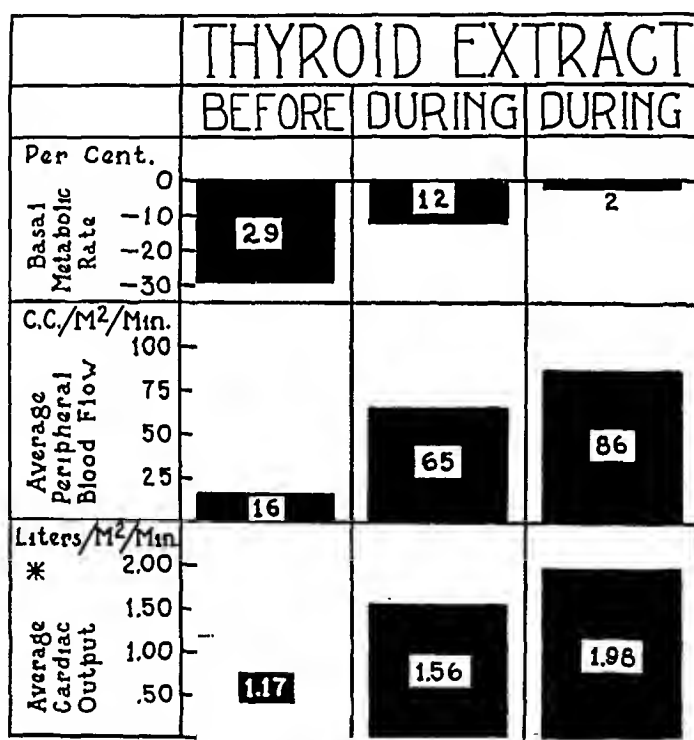


Fig. 3.—Data relating to subject L. C., who was suffering from myxedema.

rate caused by administration of thyroid extract. The average cardiac output in the group they reported, at basal metabolic rates comparable to those at which these studies of peripheral blood flow were made, is shown in Fig. 4. The allotment of the cardiac output to the various organs in man is not known. In myxedema, when the cardiac output is low, the amount allotted to the skin is now found to be decreased. At the average basal metabolic rate of -30 per cent, about 1.3 per cent of the cardiac output was allotted to the skin. On the return of cardiac output to normal during thyroid extract therapy, the peripheral blood flow increased also, so that approximately 4 per cent of the output was now allotted to the skin.



\* Stewart, Deitrick & Crane

Fig. 4.—The average basal metabolic rate and the average peripheral blood flow of the six myxedema patients, together with the average cardiac output of myxedematous patients, at comparable levels of basal metabolism, taken from the data of Stewart, Deitrick, and Crane.<sup>1</sup>

The cardiac output is increased in thyrotoxicosis<sup>11</sup> and decreases with the administration of iodine and again after subtotal thyroidectomy. Stewart and Evans<sup>5</sup> measured the cardiac output in one patient, A. S. (History No. 230995), who was suffering from hyperthyroidism, in order to correlate it with the peripheral blood flow. The procedure was exactly the same as that followed by one of us on another occasion.<sup>1</sup> Before giving iodine, at a time when the basal metabolic rate was +60 per cent, there was an allotment of 6 per cent of the

cardiac output to the peripheral circulation. During iodine therapy, and again after operation, when the basal metabolic rates were +18 and +6 per cent, respectively, the amounts of blood allocated to the periphery were 5 and 3 per cent, respectively, of the volume output of the heart.<sup>5</sup>

From Stewart, Deitrick, and Crane's observations,<sup>1</sup> it appeared that the cardiac output per minute and per beat was decreased to such an extent in the myxedematous state that, in order to maintain an adequate circulation even for the lowered metabolic requirements of the organism, an increase in the arteriovenous oxygen difference took place. The observations now being reported demonstrate that the amount of blood allotted to the periphery was small when the patients were suffering from myxedema (Fig. 4). Increased blood flow to the surface indicates increased heat loss. These data suggest that the mechanism responsible for the circulatory phenomena of thyroid insufficiency acts to conserve heat, for not only was the total cardiac output and that portion allocated to the body surface decreased, but the velocity of blood flow was so slow that the arteriovenous oxygen difference was increased. Boothby and Rynearson<sup>11</sup> observed that, in thyrotoxicosis, there was a greater increase in cardiac output than occurred in normal subjects as a result of a corresponding increase in oxygen consumption due to work. It was shown that during this time the arteriovenous oxygen difference was decreased. Recent observations of Stewart and Evans<sup>5</sup> showed a marked increase in peripheral blood flow during the hyperthyroid state. Since the total cardiac output and peripheral blood flow were greater than those required for tissue metabolism (decreased arteriovenous oxygen difference), the increased peripheral blood flow in thyrotoxicosis served to increase heat loss, whereas the decreased peripheral blood flow in myxedema served to conserve heat.

In these studies, as in those on hyperthyroidism,<sup>5</sup> the circulation time was estimated in order to have an additional objective measurement to correlate with peripheral blood flow. The results demonstrate that, in the myxedematous state, when the basal metabolic rate and peripheral blood flow were decreased, the circulation time was prolonged. With a progressive increase in the former during the administration of thyroid extract, there was a progressive decrease in circulation time (Tables I and II) (Fig. 1). These results were the reverse of those found in cases of hyperthyroidism (Table II).<sup>5</sup>

#### SUMMARY

A method described in previous papers<sup>5, 6</sup> was used. Measurements were made of peripheral blood flow in six patients suffering from myxedema and were compared with similar observations of Stewart and Evans<sup>5</sup> on six subjects who had hyperthyroidism. The myxedematous subjects were studied before treatment and on several occasions during

the course of administration of thyroid extract. In addition, certain other measurements of the circulation were recorded. The results may be summarized as follows:

1. In the myxedematous state, when the basal metabolic rate was low, the peripheral blood flow in cubic centimeters per square meter per minute was decreased. With a progressive increase in basal metabolic rate to normal levels during the administration of thyroid extract there was a progressive increase in peripheral blood flow, so that a linear relationship was maintained. On the other hand, as the basal metabolic rate decreased with therapy in the thyrotoxic subjects, there was a progressive decrease in peripheral blood flow; here again, a linear relationship was present. When the peripheral blood flow of the patients of both groups was plotted against basal metabolic rate, the line for the myxedema patients was a rough continuation of the hyperthyroid one; the intercepts with the zero line, however, were slightly different.

2. Since there is a decrease in cardiac output in myxedema and an increase in hyperthyroidism, a smaller than normal amount of blood appears to be available for distribution to the skin in the myxedema patient, and a greater amount in the hyperthyroid one.

3. The circulation time was prolonged in myxedema and short in thyrotoxicosis. When appropriate treatment was instituted, the circulation time returned to normal in each disease.

4. In myxedema the pulse rate and pulse pressure followed roughly the increases in basal metabolic rate and peripheral blood flow. In subjects with hyperthyroidism the fall in pulse rate and pulse pressure roughly paralleled decreases in basal metabolic rate and peripheral blood flow.

5. For the most part, average skin temperature followed the changes in basal metabolic rate and peripheral blood flow in each disease. Similar trends were observed in the temperature of the hands and feet. No direct relationship was established, however, between average skin temperature and the temperature of the hands and feet.

6. No constant or significant changes in rectal temperature were observed in either disease during the several periods of study of each subject.

7. Conservation of heat in myxedema and increased heat dissipation in thyrotoxicosis have been suggested as an explanation for the marked decrease in peripheral blood flow in the former and its increase in the latter.

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#### DISCUSSION

DR. WILLIS F. EVANS, New York, N. Y.—There is nothing further that I have to add, except that I should like to comment briefly on heat conservation in myxedema and heat dissipation in hyperthyroidism—points which the allotted time this afternoon would not permit.

During thyroid insufficiency the cardiac output is low, and the studies just reported show that the amount of blood allotted to the periphery is small (about 1 per cent before treatment and approximately 4 per cent after giving adequate amounts of thyroid extract). In addition, the arteriovenous oxygen difference is increased, and the velocity of blood flow is decreased in this disease. These data suggest that the mechanism responsible for the circulatory changes in myxedema conserves heat, for not only are the total cardiac output and that portion allotted to the periphery decreased, but the velocity of blood flow is so slow that, in order to maintain an adequate circulation even for the lowered metabolic requirements of the organism, an increase in the arteriovenous oxygen difference takes place.

Graves' disease stands at the opposite end of the metabolic scale. We have made measurements of the cardiac output and peripheral blood flow in one patient suffering from Graves' disease. We found that before treatment the amount of blood allotted to the periphery was approximately 6 per cent of the total cardiac output, whereas, after subtotal thyroidectomy, the allotment was only 3 per cent of the cardiac output. The cardiac output in Graves' disease is increased above the metabolic requirements of the tissues. This has been demonstrated by Boothby and Rynearson, who attributed this change to some sympathetico-stimulating substance circulating in the blood. Moreover, the arteriovenous oxygen difference is decreased in thyrotoxicosis at a time when the cardiac output is increased out of proportion to the basal metabolic rate. Increased blood flow to the surface brings about increased heat loss, and it is to this end that the circulation appears to be changed in thyrotoxicosis, for in this disease the total cardiac output and peripheral blood flow are greater than is required for tissue metabolism, as indicated by a decreased arteriovenous oxygen difference.

# A STUDY OF THE RATE OF WATER LOSS FROM THE SURFACES OF THE FINGER TIPS AND TOE TIPS OF NORMAL AND SENILE SUBJECTS AND PATIENTS WITH ARTERIAL HYPERTENSION

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THE role of the sympathetic nervous system in the pathogenesis of arterial hypertension has not been adequately defined. There is evidence to show that there may be an increase in sympathetic tone.<sup>1, 2</sup> Most of these observations have been limited to the influence of the sympathetic nervous system on the cardiovascular system. The degree of sympathetic activity, especially in patients with arterial hypertension, may be estimated by measuring the rate of water loss from the skin. Such studies seem not to have been undertaken. It has been widely observed that resting and apparently comfortable patients with hypertension have cold and clammy extremities and that cutting certain sympathetic nerves leads to dryness of the extremities, but this has been observed likewise in other people. It was thought that quantitative measurements of the rate of sweating in normal and senile subjects and in patients with hypertension might throw light on the role of the sympathetic nervous system, and these investigations were therefore undertaken.

## METHOD

The method used in these studies has already been described.<sup>3</sup> It consists essentially of passing dry oxygen through chambers covering the skin of fingers and toes, and then conducting the moisture-laden oxygen through cold coils. From the difference in weight of the coils before and after the passage of oxygen, the amount of water lost is learned. First, the subjects rested for thirty minutes in a special room<sup>4</sup> (temperature 75° F.  $\pm$ 1°, relative humidity less than 50 per cent). This room was designed to remove all the appearances of a laboratory. The subjects were alone and undisturbed throughout the periods of observation; collections of sweat, weighing, and other manipulations were carried out in an adjoining room, separated from the subject's room by a sound-proof wall. The collections were made continuously for sixty minutes at fifteen-minute intervals. These observations were made during the last week of March, April, and the first two weeks of May, 1941.

From the Hospital of the Rockefeller Institute for Medical Research, New York.

This is the fourth paper reporting the results of studies of the small blood vessels and related subjects.

Read before the Vascular Section, American Heart Association, Cleveland, May 30, 1941.

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\*Commonwealth Fund Fellow.

There were thirteen normal subjects whose ages ranged from 8 to 44 years, ten patients with arterial hypertension who were free from renal or cardiac failure and were between 27 and 54 years of age, and eight senile subjects who were free from renal or cardiac failure and were normal except for the usual manifestations of senility. The ages of the senile subjects varied from 70 to 85 years. In addition, a miscellaneous group was studied. These observations included measurements on two subjects with hypertension which were made before, and three weeks after, bilateral sympathectomy (ninth thoracic sympathetic nerve to first lumbar, and the celiac and aortic renal plexuses), on a subject with advanced Raynaud's disease and scleroderma, and on a normal subject, continuously, for a period of 12.25 hours, and also simultaneous measurements on four groups of two subjects each, in separate beds in the same room.

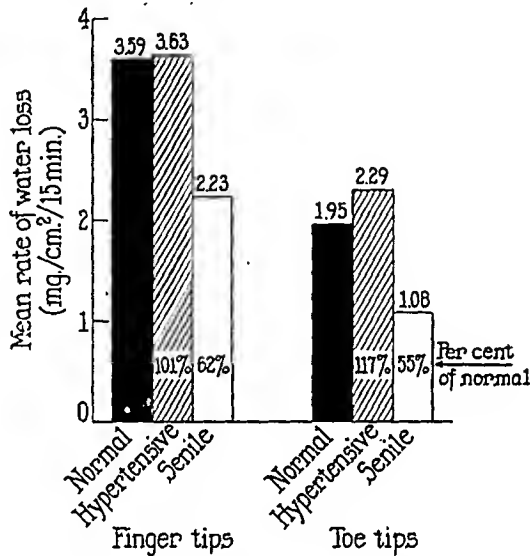


Fig. 1.—Mean rates of sweating of the tip of the right index finger and right second toe of groups of resting normal, hypertensive, and senile subjects.

The measurements were made simultaneously on the tip of the right index finger and right second toe of all subjects. In some instances it was the left index finger or left second toe (or both) that was examined simultaneously with the right ones. The areas of the finger and the toe nails were subtracted from the respective total areas of the parts examined, so that the results apply to the effective area only. The total areas were measured as previously described,<sup>3</sup> and the areas of the nails, by measuring the area of paper necessary to cover the nails of the positive casts of the parts. The temperature of the oxygen surrounding the parts in the chambers was 75° F., and the relative humidity, approximately zero. The temperature of the air surrounding the adjacent parts was 75° F., and the relative humidity, 50 per cent. In order to ascertain the influence of the dry oxygen on the rate of water loss from the parts enclosed in the chambers, observations were conducted in which room air and dry oxygen were used alternately to collect the water given off by the enclosed parts. It was found that the rate of water loss was the same whether the relative humidity was approximately zero or near 50 per cent.

### RESULTS

The mean rate of water loss from the tips of the index fingers of the normal subjects was 3.59 mg. per square centimeter per fifteen minutes; the minimum and maximum variations were 1.84 and 6.96, respectively.

RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) MEASURED SIMULTANEOUSLY ON THE RIGHT INDEX FINGER AND RIGHT SECOND TOE TIP OF 13 NORMAL, WHITE, RESTING ADULTS

[illegible]





The mean rate from the toe tips was 1.95 mg.,\* and the minimum and maximum variations were 0.67 and 6.81, respectively (Table I).

In the patients with arterial hypertension the loss from the finger tips was 3.63 mg., with minimum and maximum variations of 1.75 and 8.80, respectively, and, from the toe tips, 2.29 mg., with minimum and maximum variations of 0.62 and 6.12, respectively (Table II).

In the senile subjects the loss from the finger tips was 2.27 mg., with minimum and maximum variations of 1.71 and 2.87, respectively, and, from the toe tips, 1.08 mg., with minimum and maximum variations of 0.68 and 1.55, respectively (Table III, Fig. 1).

The loss in patients with hypertension was essentially the same, therefore, as in normal subjects. The senile subjects, on the other hand, lost much less. In all groups the loss from the toe tips was practically one-half that from the finger tips; the variations were from 32 to 99 per cent but were much less in the senile groups.

TABLE IV

RATE OF SWEATING (MG./SQ. CM. SKIN AREA/15 MIN.) OF FINGER TIPS (F) AND TOE TIPS (T) OF PAIRS OF NORMAL, RESTING SUBJECTS, STUDIED SIMULTANEOUSLY

| SUBJECT NO. | DATE    | PART | AREA OF SKIN (SQ. CM.) | FIRST 15 MIN. | SECOND 15 MIN. | THIRD 15 MIN. | FOURTH 15 MIN. | MEAN 15 MIN. |
|-------------|---------|------|------------------------|---------------|----------------|---------------|----------------|--------------|
| 6 and 96    | 5 /6/41 | F    | 8.64                   | 1.31          | 1.23           | 1.71          | 1.28           | 1.38         |
|             |         | T    | 8.60                   | 1.86          | 0.70           | 1.17          | 1.05           | 1.20         |
|             |         | F    | 6.90                   | 2.97          | 2.59           | 3.12          | 8.74           | 4.37         |
|             |         | T    | 6.84                   | 1.64          | 1.75           | 2.19          | 3.01           | 2.15         |
| 14 and 86   | 5/ 7/41 | F    | 7.56                   | 4.03          | 3.66           | 2.76          | 2.74           | 3.30         |
|             |         | T    | 7.98                   | 1.56          | 1.04           | 1.13          | 1.17           | 1.23         |
|             |         | F    | 7.62                   | 3.33          | 2.93           | 2.23          | 1.84           | 2.58         |
|             |         | T    | 7.96                   | 1.62          | 1.34           | 0.72          | 0.67           | 1.09         |
| 86 and 49   | 5/13/41 | F    | 7.62                   | 3.18          | 5.59           | 2.81          | 5.46           | 4.26         |
|             |         | T    | 7.96                   | 1.42          | 1.46           | 1.09          | 0.89           | 1.22         |
|             |         | F    | 8.66                   | 5.57          | 4.50           | 3.46          | 2.75           | 4.07         |
|             |         | T    | 8.44                   | 2.71          | 2.30           | 1.67          | 1.34           | 2.00         |
| 54 and 96   | 5/16/41 | F    | 9.08                   | 8.37          | 7.02           | 7.16          | 5.54           | 7.02         |
|             |         | T    | 8.29                   | 2.24          | 1.62           | 1.91          | 1.91           | 1.92         |
|             |         | F    | 6.90                   | 4.35          | 2.78           | 3.52          | 3.43           | 3.52         |
|             |         | T    | 6.84                   | 1.55          | 1.37           | 1.21          | 0.91           | 1.26         |

There were marked variations in the rate of sweating from person to person, and from fifteen-minute period to fifteen-minute period in the same person. The variation from period to period was greatest in normal and hypertensive subjects and least in the senile ones. In fact, the senile subjects were noteworthy for their constancy. In one of the subjects (Subject 86, Table IV) the mean rate of sweating of the finger tip was only three-fifths as rapid on one day as it was six days later, whereas in the toe tip it was only slightly less. The variations were always much greater in the fingers than in the toes. Similar results were obtained on Subject 96 (Table IV).

\*The calculation is always given in milligrams per square centimeter per fifteen minutes.

When normal subjects were studied simultaneously in pairs, the rate of water loss increased in the finger or toe, or both, of one, while it remained the same or actually decreased in the other (Table IV). The variations from part to part in each of the pairs of subjects were discordant. The rate of sweating of the right and left index fingers or the right and left second toes also varied discordantly (Table V).

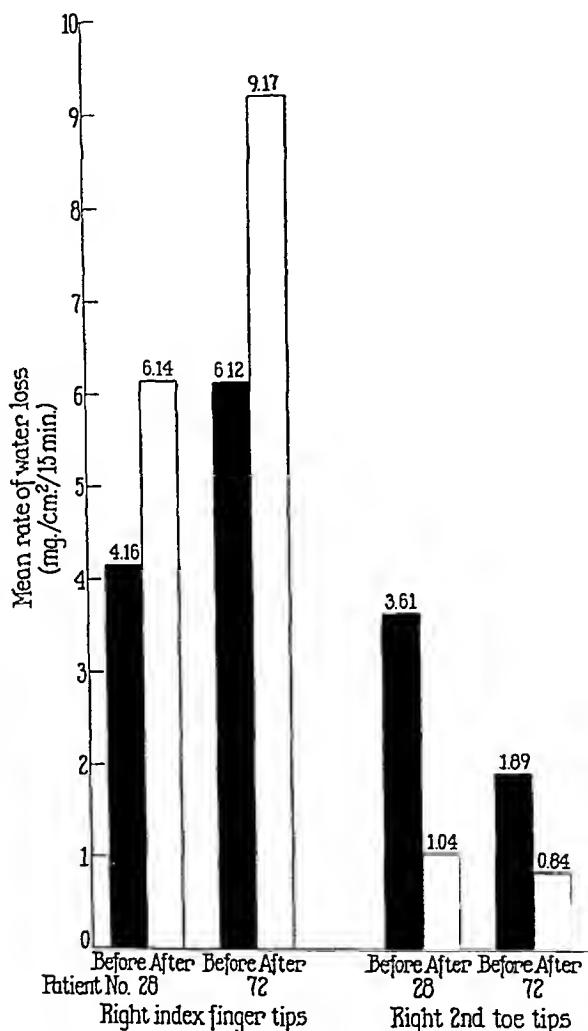


Fig. 2.—The rate of sweating of the tips of the fingers and toes of two hypertensive subjects before, and three weeks after, bilateral sympathectomy (ninth thoracic sympathetic nerve to first lumbar and the celiac and aortic renal plexuses).

In hypertensive patients whose lower thoracic and lumbar sympathetic nerves had been cut and the coeliac and aortic renal ganglia excised, a decrease of more than half the rate of water loss from the second toe and an increase of about half the rate from the index finger were found (Fig. 2). These differences were great enough for subjects and observers to detect by qualitative methods.





There were great variations in the rate of sweating of the finger and toe tips of a normal subject when measurements were made continuously for 12.25 hours, with collections every fifteen minutes (Fig. 3). Shortly after each meal (noon and evening), the rate increased for about ninety minutes. When the subject fell asleep, it reached a minimum which was very constant.

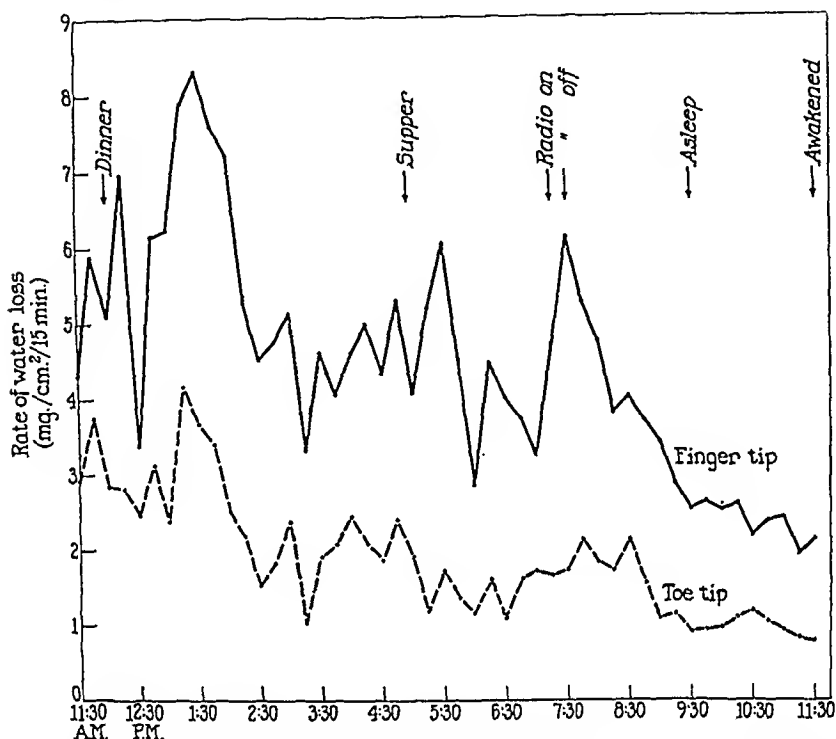


Fig. 3.—Changes in the rate of sweating measured for fifteen-minute periods during an observation of 12.25 hours.

The rate of water loss of a patient with advanced Raynaud's disease and scleroderma of the upper extremities whose cervical sympathetic nerves had been cut eight years before was 1.12 mg. in the right, and 1.25 mg. in the left, index finger tip per square centimeter per fifteen minutes. These rates were about one-third as rapid as in the same parts of normal subjects, and less than the normal minimum value. The rate of water loss from the right second toe tip was 1.85 mg. per square centimeter per fifteen minutes, a value similar to that of the normal group. Early Raynaud's disease of the toes was present in this patient.

#### DISCUSSION

The values for the rate of water loss from the tips of the fingers and toes of normal subjects are greater than in those previously reported.<sup>3</sup> In the first series of normal persons the loss from the fingers was 2.10 mg. per square centimeter per fifteen minutes, and, from the toes, 1.42

(calculated for the area of the skin, not the total surface area), whereas, in the present series of normal subjects, it was 3.59 from the fingers and 1.95 from the toes. Many of the subjects were studied in both series. The conditions were the same except for two factors: (1) The first study was conducted during the hot months of June, July, and August, 1940, and the present study, during the cool period of the last week of March, April, and the first two weeks of May, 1941. Although the temperature and humidity of the room were the same, subjects who entered the room during the hot summer months invariably commented on the coolness of the room, whereas those who entered this spring failed to make such comments. In fact, most of the subjects considered the room warm. That this is an important cause for the differences is not supported by the studies of Winslow, Herrington, and Gagge,<sup>5</sup> who stated: "During the summer season, the mechanism of sweat secretion is in better working order than in winter so that the body responds to a given condition (in the zone of evaporation regulation) with a somewhat higher secretory activity." More extensive studies, over a period of a year, would, nevertheless, be necessary before a definite conclusion regarding seasonal influences could be reached. (2) In the first series, psychic disturbances played a role because of the presence of laboratory equipment in the same room with the subjects; this was markedly reduced in the second series.<sup>4</sup> The importance of this factor could not be estimated, but it is true that many of the subjects were well acquainted with the laboratory and were not likely to be upset by it. There are many variables, however, in a person's daily and yearly activities that may be the basis of physiologic differences. The studies on patients were interspersed with those on the normal persons of the present series, and all observations were completed before the summer season began.

The marked variations in the same person from time to time and from one anatomic region to another at the same time were expected. The number of sweat glands which function at a given time is, as is well known, quite variable.<sup>5, 6</sup> Sweating is influenced by many factors, including the psyche and fatigue, both of which lack uniformity, and both of which are always exerting some influence in any physiologic study on conscious persons.

In two subjects who were studied in the same room, in separate beds, under identical environmental conditions, there were discordant variations in their comparable anatomic parts (Table V). Such variations must be the result of conditions unrelated to the room. Furthermore, although the mean rate of sweating in the toes was always essentially one-half the mean rate in the fingers, this was not true for each individual measurement. The ratio of the rates of sweating in fingers and toes in any one subject varied markedly.

Under the conditions of our observations, the palmar surfaces of the hands were noticeably moist when the rate of water loss from the finger tip was 5 mg. or more.

The mean rate of sweating in the patients with hypertension was about the same as that in the normal subjects. This fact is interpreted to mean that, under conditions of rest and quiet, the sympathetic tone, as indicated by its effect on sweating, is about the same in hypertensive as in normal persons. This is in keeping with the observations of others who studied the cardiovascular system and found no evidence of increased sympathetic tone.<sup>1, 2</sup> Under conditions of stress and strain an increase may nevertheless exist.

The rate of sweating in the senile subjects was definitely less rapid and much less variable than in the normal persons. This is probably one of the general manifestations of reduced physiologic activity which are known to occur in senile persons. No attempt was made to learn what part this was of their total capacity to sweat. It is unknown whether the low rate of sweating is due to a decrease in the number of sweat glands, to partial atrophy, to decreased function, or to all three factors.

#### SUMMARY

The rate of water loss from the tip of the index finger and second toe of normal subjects was very variable. There were variations from one period of fifteen minutes to another, from finger to toe, from right finger to left finger, and from day to day in the same subject. The mean rate of sweating in the toe tips was approximately one-half that in the finger tips, although this ratio could be variable. The rate of sweating varied markedly from person to person under identical conditions of observation.

In the patients with arterial hypertension the rate and variations of water loss from the finger and toe tips were about the same as in the normal subjects. This suggests that, in resting persons with hypertension, sympathetic activity is no greater than in normal subjects.

In senile subjects the rate of water loss was much less than in the normal subjects and patients with hypertension. Furthermore, the rates from period to period were much less variable. In fact, the senile subjects were outstanding for the constancy with which they lost water. This may be part of the reduced physiologic activity which is known to occur in senile persons.

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## INFECTED THROMBI OF THE HEART

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DURING the past two and one-half years we have encountered at the New York City Hospital, Welfare Island, several cases of septic thrombosis of the heart. The thrombi differed from the usual septic mural thrombi in that they were not associated with acute bacterial endocarditis, valvular or mural. In the majority of cases, they occurred in patients who came under observation because of cardiac failure. In several instances it was possible to ascertain the original site from which the pyogenic organisms reached the heart. Since we were unable to find in medical literature any mention of similar cases, and because this lesion offers an explanation of cardiac failure in some patients, this series is being reported. During the same period, several other thrombi were investigated from the bacteriologic standpoint with negative results.

### CASE REPORTS

CASE 1.—The patient, a young Negro, aged 31 years, was admitted to the medical service of Dr. B. F. Donaldson Feb. 4, 1939, with severe congestive failure. For three years he had been under observation at various institutions because of congestive failure due to rheumatic heart disease. The final phase began one week before he entered the New York City Hospital. The course was rapidly progressive; the temperature ranged from 97.6° to 101° F.; tachycardia and a pulse-temperature discrepancy were constant; and jaundice developed. The electrocardiogram showed normal sinus rhythm, a rate of 100, a P-R interval of 0.24 sec., no axis deviation; T<sub>1</sub> and T<sub>2</sub> were diphasic, and QRS was slurred. On the third hospital day sudden cardiac collapse appeared, and death followed in one hour.

*Autopsy* (5436).—The heart weighed 525 Gm. In the right auricular appendage there were numerous soft, round, yellow thrombi, with dirty yellow fluid contents, from which a hemolytic *Staphylococcus aureus* was cultured. The auricular muscle showed extensive, acute necrosis, but bacteria were not demonstrable in sections. Mitral stenosis was present (healed), and the aortic valve was the seat of a chronically active lesion. The left ventricle showed several Aschoff bodies. The upper lobe of the right lung was the seat of an acute, embolic, suppurative pneumonia; cultures were not taken.

CASE 2.—The patient, a white man, aged 74 years, was admitted to the medical service of Dr. B. F. Donaldson March 22, 1939. He had had mild dyspnea on exertion and edema of the ankles for one year. For three weeks the symptoms had been much more severe. He was acutely ill and jaundiced and was edematous up to the abdominal wall. The heart was enlarged; the sounds were of fair quality;

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the rate was rapid; and the beating was irregular. The blood pressure was 140/80. The course was progressive, with rising temperature, tachycardia, increasing weakness of the pulse, pulmonary signs not very suggestive of pneumonia, and death on the third day. A pulse-temperature discrepancy was present from the beginning and increased steadily; during the last thirty-six hours the pulse was too rapid and weak to count accurately.

*Autopsy* (5488).—The heart weighed 675 Gm. In the right auricular appendage were a few globular, soft thrombi which contained creamy yellow pus; the culture yielded pneumococcus Type III. In the underlying myocardium there were numerous foci of degeneration, with polymorphonuclear infiltration and Gram-positive cocci. The ventricular muscle showed extreme cloudy swelling, without cellular reaction. The coronary arteries were moderately sclerotic. The right lung was the seat of an acute lobar pneumonia (upper and lower lobes). The lung was not cultured, but the bacteria which were seen in the sections looked like pneumococci.

CASE 3.—The patient, a white man, aged 48 years, was under observation on two occasions. He was first admitted to the medical service of Dr. J. H. Cudmore on Feb. 10, 1939, because of dyspnea on exertion, weakness, and headaches. The onset was five weeks previously. High blood pressure had been discovered one year before. There were moderate cyanosis, an enlarged heart with good sounds, a blood pressure of 195/130, a low fever (100.4° F.), a pulse rate of 112, and albuminuria (1 plus). The renal function tests showed moderate inability to concentrate. The nonprotein nitrogen content of the blood was 33 mg. per cent. The electrocardiogram showed normal sinus rhythm, a rate of 100, and right axis deviation; T<sub>1</sub> was of low amplitude, and QRS was slurred. He had one severe attack of nocturnal dyspnea, with intense cyanosis. Signs of bleeding duodenal ulcer appeared, necessitating transfusion. After seven weeks he improved and was discharged (March 29, 1939).

He was readmitted May, 19, 1939, to the medical service of Dr. John Carroll. The cardiac symptoms had recurred after two weeks and were accompanied by failing vision. The most prominent features throughout the final period of observation of ten weeks were paroxysmal dyspnea, cyanosis, and increasing anemia. On one occasion there was a tarry stool. The blood pressure remained elevated. The urine had a fixed specific gravity of 1.010, and contained casts, erythrocytes, and leucocytes. The nonprotein nitrogen rose from 35 to 150 mg. per cent. The Van Slyke index dropped to 17 per cent. The electrocardiogram showed normal sinus rhythm, a rate of 107, a P-R interval of 0.16 sec., and no axis deviation. T<sub>1</sub> was broad; T<sub>2</sub> and T<sub>3</sub> were depressed; and QRS was slurred. The temperature varied from 99° to 100° F.; during the last few days it gradually rose to 102° F. The pulse was consistently rapid, and there was a constant pulse-temperature discrepancy. Death occurred in coma on July 28, 1939.

*Autopsy* (5579).—The heart weighed 600 Gm. The right auricular appendage contained two large, soft, purulent thrombi, from which Type III pneumococcus was isolated. The underlying muscle was acutely necrotic. In the left ventricle there were several acute miliary infarcts and small abscesses. There was a bilateral acute, lobar pneumonia, and the sections showed bacteria which resembled pneumococci.

CASE 4.—The patient, a 44-year-old Negro, was admitted to the medical service of Dr. Charles Dillon on June 9, 1939, where she remained until her death on September 2. Her illness dated back two years and was characterized by a steadily progressive cough, with sputum which was neither bloodtinged nor foul, weight loss, and dyspnea on exertion. The physical signs were largely cardiac. The heart

was enlarged; the neck veins were engorged; the liver was tender and enlarged; and the blood pressure was 220/150. During July there was a period of profuse perspiration, dyspnea, equivocal signs at the base of the right lung, bloodtinged sputum, low-grade fever, and rise of the nonprotein nitrogen to 60 mg. per cent. One attack of severe angina occurred. With diminution of the amount of sputum, the lung signs became more definite. The last six weeks were characterized by neurological manifestations, namely, permanent urinary and fecal incontinence, variable lethargy, Cheyne-Stokes respiration, and periods of quiet delirium. The nonprotein nitrogen level fell to 32 mg. per cent. The blood pressure remained high. Death occurred in coma. During the last few hours the pulse became almost imperceptible.

*Autopsy* (5602).—The heart weighed 400 Gm. There was an acute diffuse periecarditis. A gray, purulent, mural thrombus was present in the right auricle, cultures from which revealed staphylococci and streptococci. The auricular muscle was acutely damaged, and in the left ventricle there were a few miliary infarcts. The lower lobe of the right lung contained a chronic, putrid abscess, and many of the veins at the periphery of this abscess were thrombosed. The organisms isolated were the same as those found in the heart. The brain showed multiple, cerebral cortical hemorrhages.



Fig. 1.—Case 5. Acute thrombosis of the anterior descending coronary artery (arrow) and massive myocardial infarction. In the left ventricle there are numerous, small thrombi of the recesses, and, in the right ventricle (arrow on the left), several larger, smooth thrombi. *Streptococcus hemolyticus* was isolated from a traumatic leg ulcer and the earlobe thrombi. The mitral and aortic valves are the seat of chronic rheumatic disease.

CASE 5.—The patient, a white man, aged 44 years, was admitted to the medical service of Dr. Charles Dillon on Sept. 4, 1939, because of an anginal attack which had occurred eight days before. The first attack, one year previously, had incapacitated him for only four days. Physical examination showed an acutely ill,



dyspneic, and cyanotic man. The heart was greatly enlarged, and the first sound at the apex was split. The blood pressure was 85/65. There were râles at the bases of both lungs. The temperature was 100° F.; the pulse rate, 120; and the respiratory rate, 32. The electrocardiogram showed normal sinus rhythm, a rate of 107, normal A-V conduction time, and left axis deviation; S-T<sub>1</sub> was slightly high, and QRS was broad, notched, and slurred. There was a small ulcer on the right tibial surface which was the result of an injury received some time before. The temperature fluctuated to 102° F., and the pulse rate remained rapid (100 to 120). Death occurred suddenly on the fourth hospital day.

*Autopsy* (5605).—The heart weighed 500 Gm. It showed a chronically active rheumatic mitral and aortic valvulitis, severe arteriosclerosis of the coronary arteries, acute thrombosis of the anterior descending artery, acute massive cardiac infarction, and many smooth mural thrombi of both ventricles and the left auricle (Fig. 1). Histologically, all parts of the wall contained numerous miliary infarcts. In the lungs there were numerous recent arterial emboli and acute infarctions. Cultures of the leg ulcer and cardiac thrombi revealed *Streptococcus hemolyticus*. No bacteria were demonstrated in sections of the heart muscle or in the thrombus of the coronary artery.

CASE 6.—The patient, a white man, aged 68 years, was admitted to the medical service of Dr. W. L. Reardon Oct. 6, 1939. He had always been well until eight days previously, when he had a typical anginal attack. The heart did not appear to be enlarged; the first mitral sound was split; the blood pressure was low (80/60); the neck veins pulsated; and the liver was enlarged and tender. The electrocardiogram showed normal sinus rhythm, a rate of 93, normal A-V conduction time, and a tendency to right axis deviation. S-T<sub>1</sub> had a high take-off; T<sub>2</sub> was broad; T<sub>3</sub> was inverted; S-T<sub>4</sub> had a low take-off; and QRS was of low voltage in all leads. A pericardial friction rub appeared. Signs of pulmonary consolidation, persistent tachycardia, and a fluctuating temperature followed. Death occurred on the fifth day.

*Autopsy* (5654).—The heart weighed 500 Gm. The surface was covered by a thick fibrinous exudate. In the left auricle there was a large globular thrombus which projected into the cavity from the appendage. The coronary arteries were markedly sclerotic; the left descending branch was occluded by a recent thrombus, and there was an acute, massive infarction. *Streptococcus hemolyticus* was isolated from the pericardium, and *Streptococcus viridans* from the auricular thrombus. Histologic examination showed numerous miliary infarcts in the walls of both auricles. The lungs were the seat of acute confluent bronchopneumonia.

CASE 7.—The patient, a white woman, aged 24 years, was admitted to the medical service of Dr. W. L. Whittemore Oct. 18, 1939. She had been under observation at another institution because of a birth injury. On Sept. 6, 1939, an exploratory laparotomy was performed at another hospital, and tuberculous peritonitis was found. After her discharge she developed a cough and then entered New York City Hospital. She appeared acutely ill. Her lungs were filled with râles. The surgical incision was healed, but the abdomen was tense and slightly tender. The heart rate was 118, and the blood pressure, 85/60. Toward the end of the month there were frequent attacks of paroxysmal dyspnea. On the twelfth hospital day, evisceration through the incision occurred. The temperature ranged from 98° F. to 102° F. The pulse remained rapid and there was an increasing pulse-temperature discrepancy. Death occurred on Nov. 11, 1939.

*Autopsy* (5665).—The heart weighed 350 Gm. The myocardium was flabby and muddy in color. There were numerous purulent mural thrombi in both auricles, and the left ventricle contained a large thrombus which extended from apex to base

(Fig. 2). *B. coli* was cultured from these thrombi. Histologic examination showed acute interstitial myocarditis which was most marked in the deeper layers of muscle. The base of the right auricular thrombus was beginning to organize. In addition, there were tuberculosis of the peritoneum, mesenteric lymphatics, cecum, and lungs, and acute peritonitis due to fecal contamination.



Fig. 2.—Case 7. Acute infected thrombi of the left ventricle and right auricle. In the left ventricle they extend from apex to base; in the right auricle they are multiple. Similar thrombi were present in the left auricle. *B. coli* was isolated. The cardiac infection was secondary to acute peritonitis, superimposed, by fecal contamination, on a tuberculous peritonitis.

CASE 8.—The patient, a white woman, aged 74 years, was admitted Dec. 21, 1939, to the neurologic service of Dr. John Nolan because of a left-sided hemiplegia of thirty-six hours' duration. She improved steadily until Feb. 9, 1940, when she developed a Type XXI pneumococcal pneumonia. Sulfapyridine was given, and the temperature returned to normal in three days. Four days later the temperature again rose, reaching 105.6° F.; chemotherapy was ineffectual, and death occurred about thirty-six hours later. The pulse rate and temperature remained in normal proportion.

*Autopsy* (5776).—The heart weighed 275 Gm. The myocardium was flabby and of poor color. Near the apex of the left ventricle there were three rounded, friable, yellow, mural thrombi, with necrotic centers. Nearby was a firmer pink-white thrombus (Fig. 3). Cultures revealed a non-chain-forming, Gram-positive coccus which failed to grow on subculture and could not be identified. Histologically, the ventricular muscle showed a few areas of miliary necrosis. The left lung was the seat of a patchy, acute bronchopneumonia which yielded Type XXI pneumococcus.

CASE 9.—The patient, a 68-year-old white man, was admitted with severe congestive failure to the medical service of Dr. W. L. Whittemore on Dec. 7, 1940. For seven years he had suffered from gradually increasing dyspnea which had resulted in little inconvenience. In February, 1940, he had a frank anginal attack. One week before entering the hospital he had a second very severe attack and became bedridden. He was very dyspneic and cyanotic. The neck veins pulsated, and the apex beat could not be palpated. The ventricular rate was 140 and regular, and the pulse rate was 120. There was dullness at the base of the left lung. The edge of the liver was hard and was palpable at the level of the umbilicus. The blood pressure was 90/80. Albuminuria was present, and the nonprotein nitrogen was 106 mg. per cent. The electrocardiogram showed normal sinus rhythm, a rate of 75, normal A-V conduction time (0.16 sec.), and no axis deviation.  $T_1$  was inverted;  $T_2$  and  $T_3$  were of low amplitude; and there was slurring of QRS. Bilateral hydrothorax and ascites appeared, and death occurred from pulmonary edema after five days. The temperature rose only to 100.2° F. terminally. The pulse remained rapid (80 to 132) and was variable in force.

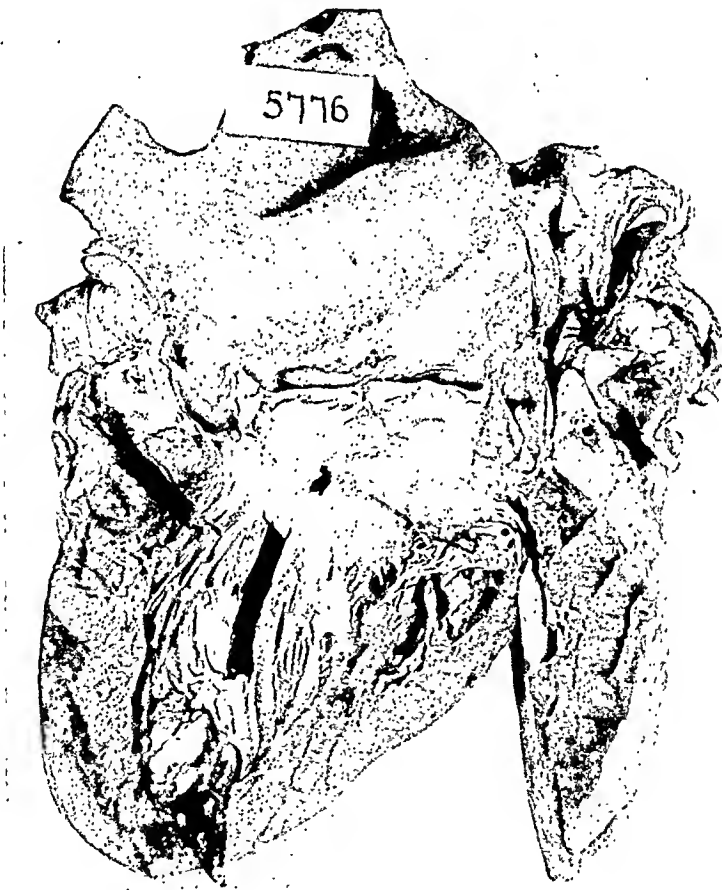


Fig. 3.—Case 8. Infected thrombi of the apex of the left ventricle, associated with Type XXI pneumonia. Non-chain-forming coccus was isolated from the thrombus, and pneumococcus Type XXI, from the lung.

*Autopsy* (6021).—The heart weighed 650 Gm. Both auricles contained sessile and pedunculated thrombi in the appendages and main chambers; the largest was 2 cm. in diameter. Their contents were dark red and slightly viscid and yielded

streptococci on culture. The underlying muscle was extensively necrotic and diffusely infiltrated with polynuclear cells. The left ventricle had a mottled appearance due to acute miliary infarctions. The coronary arteries were markedly sclerotic. An old, recanalized thrombus was present in the anterior descending branch. There was a bilateral, acute bronchopneumonia, from which streptococci were isolated.



Fig. 4.—Case 11. Multiple thrombi of right auricle. *Streptococcus hemolyticus* and *B. coli* were isolated from the peritoneal exudate, septic pulmonary emboli, and cardiac thrombi.

CASE 10.—The patient, a white woman, aged 69 years, was admitted in coma on Feb. 7, 1941, to the medical service of Dr. B. F. Donaldson. One week before admission coma occurred suddenly, followed by a short period of recovery and a recurrence. Physical examination was essentially negative except for an enlarged heart and a blood pressure of 140/110. The course was that of fluctuating coma. Death occurred on the fifth day. The temperature rose from 99° F. to 104° F. The pulse rate remained in normal relation to the temperature.

*Autopsy* (6071).—The heart weighed 350 Gm. There were numerous soft, round, mural thrombi in the left ventricle, from apex to base, arising between the columnae carneae. The contents were fluid and yielded a non-chain-forming coccus on culture. The coronary arteries were markedly sclerotic, and the left circumflex branch was occluded by an old, recanalized thrombus. Histologically, the unscarred portion of the ventricle showed numerous acute, miliary infarctions. There were a bronchogenic carcinoma, acute lobular pneumonia, marked cerebral arteriosclerosis, and a small cerebral infarction.

CASE 11.—The patient, a 66-year-old Negro, was admitted April 25, 1941, to the surgical service of Dr. F. Bancroft because of chronic ulcers of the legs. The only additional features were a severe anemia, an enlarged heart, and a blood pressure of 168/80. On May 6, she complained of abdominal pain, vomited, and had an

ill-defined, slightly tender mass in the right lower quadrant. The anemia became more severe. Signs of obstruction appeared; the temperature fluctuated to 102.4° F.; and the pulse became rapid. Death occurred in one week. During the last forty-eight hours the pulse rate became so rapid that it could not be counted accurately.

*Autopsy* (6167).—The heart weighed 485 Gm., and was covered by a fibrinous exudate. In the right auricle there were numerous soft, friable, mural thrombi (Fig. 4). The myocardium was a pale yellowish-brown. The coronary arteries were slightly sclerotic. There were several miliary infarcts in the left ventricle. The lungs showed multiple, acute, arterial emboli and acute infarctions. Acute, general peritonitis, secondary to acute appendicitis, with rupture, and a periappendiceal abscess were found. Cultures from the peritoneum, pulmonary emboli, and cardiac thrombi revealed hemolytic streptococci and colon bacilli, the former predominating.

#### DISCUSSION

Parietal thrombi of the heart are well known. According to Kaufmann,<sup>1</sup> they are usually regarded as secondary to dilatation and congestion caused by cardiac lesions, or to acute and chronic changes in the myocardium which result in slowing of, and eddy formation in, the blood current in the deep recesses, or to local degenerative changes of the endocardium. Harvey and Levine<sup>2</sup> also stated that the two most frequent causes are myocardial degeneration secondary to coronary artery disease, and improper functioning of the auricles. Although they have sometimes been described as puriform, it is generally believed that the softening is due to autolysis. An infectious type of decomposition has not been considered seriously. In the present series, pathogenic bacteria were isolated from the thrombi in each instance.

The appearance of the thrombi was striking. They were usually globular, perfectly smooth, yellow or gray in color, and soft in consistency. The contents were either frankly purulent, muddy, viscid, or sanguineous.

The sites were similar to those at which noninfected thrombi are usually found. The right auricle alone contained thrombi in five cases; the left auricle, in one, and the left ventricle, in two. More than one chamber was affected in the other five cases. Both auricles were involved once, and three chambers twice. In eight of the eleven cases the right auricle was involved, which is a higher percentage than was found by Harvey and Levine in their study of noninfected thrombi.

Bacteriologic investigations were complete in three cases. A mixture of staphylococci and streptococci was obtained in Case 4 from the lung abscess and thrombi. Streptococci were isolated from the lung and heart in Case 9. In Case 11, cultures revealed *Streptococcus hemolyticus* and *B. coli* in the peritoneal exudate, pulmonary emboli, and heart.

The bacteriologic evidence was less complete in the other cases, but necropsy supplied data which were suggestive of the original focus of infection. Case 5 was almost the same as Case 11, i.e., there were an

infection below the diaphragm, pulmonary embolism, and involvement of the heart. Hemolytic streptococci were isolated from the leg ulcer and heart; the pulmonary emboli were not cultured. In Case 1, a hemolytic *Staphylococcus aureus* was found in the heart; the lung was the seat of an embolic, suppurative pneumonia, but no culture was obtained. In Cases 2 and 3 the presence of a croupous pneumonia offered an adequate explanation for the presence of a pneumococcus in the heart. Case 8 appeared to be similar. A Type XXI pneumococcus was identified in the sputum before death and isolated from the lung at necropsy. The organism from the heart failed to grow, possibly because of the intensive chemotherapy which had been employed. Although this organism was not definitely identified, the evidence strongly suggested that it probably was a pneumococcus. In Cases 6 and 10 there was also a pneumonia, but in neither were the lungs cultured. In Case 7 there was a *B. coli* infection arising from the peritoneum, but without embolic pulmonary manifestations. We have observed in other infections caused by enteric organisms that the lungs may be unaffected, so that such a course, although not common, is not unknown. In ten of the eleven cases, therefore, the infection in the heart appeared to be secondary to the pulmonary lesion.

It is of interest to speculate upon the routes by which the heart could have become infected. The high incidence of pneumonia suggests that the original site of infection was most probably the lung, either as a primary process or as a secondary embolic pneumonia. In a recent communication, Hamman<sup>3</sup> stressed the role of embolism in acute occlusion of the large branches of the coronary arteries and mentioned thrombi of the pulmonary veins in suppurative processes. He reported one case in which there was a chronic, interlobar abscess. In the present series there were two instances of acute coronary occlusion. Suppurative pneumonia was present in Case 5, and non-necrotic pneumonia in Case 6. In neither were pulmonary thrombi observed. However, thrombi do not seem to be essential. One of us (J. R. L.)<sup>4</sup> previously reported that an infected embolus caused coronary occlusion in a case of pneumococcal pneumonia in the absence of pulmonary thrombi. The determining factor in its localization seemed to be the pre-existing, severe coronary disease. This factor was also present in both instances in this series.

An embolic mechanism may have played a part in five other cases. In Case 3 the left ventricle showed numerous military abscesses. In Case 4 there were pulmonary thrombi at the periphery of a chronic lung abscess. Acute military infarctions, with severe coronary disease, were widespread in Cases 9, 10, and 11. In Case 8, the localization of the thrombus suggested that it was arterial. In Case 7 the extensive involvement of the chambers suggested an arterial embolic spread which

was localized in the deep muscle because of the intact coronary circulation. Direct implantation from the cavities must likewise be considered seriously.

The possibility of a lymphatic spread must also be borne in mind. The rich anastomoses between the pulmonary lymphatics and the lymphatics at the base of the heart are well known and may constitute a route by which the heart can become involved secondary to pulmonary disease. We have often observed, at autopsies in this laboratory, an early pericarditis localized over the right auricle in cases of acute pneumonia. The thin auricular wall could easily become diffusely invaded, leading to the formation of an infectious thrombus. In the present series, the right auricle was affected more frequently than any other chamber.

The syndromes were entirely cardiac in five cases. In Cases 5, 6, and 9 there was angina; the pulmonary lesions were interpreted as secondary to the heart failure. No importance was attached to the leg ulcer in Case 5. Mild congestive failure had been present in Case 2 for a year, but the course was rapid during the last three weeks of life. When pneumonia attacks a patient with coronary sclerosis, it may precipitate acute cardiac failure, but it frequently is interpreted as a manifestation, not as the cause, of the failure. The same interpretation probably applies to Case 1. Such a course frequently is seen in cases of rheumatic heart disease, but the extent of the rheumatic myocarditis alone did not explain adequately the manifestations in this case.

In Case 3 the syndrome was both renal and cardiac. Death was caused by uremia. The lobar pneumonia was probably a terminal affair and enhanced the cardiac symptoms by the production of infarcts and abscesses.

The patients with abdominal disease presented symptoms which were masked partially by the surgical conditions. In Case 7, paroxysmal dyspnea and increasing tachycardia were prominent. Only an increasing weakness of the pulse and persistent tachycardia were noted in Case 11.

The patient with a pulmonary abscess (Case 4) first came under observation for severe cardiac failure, from which she apparently recovered. The pathologic changes in the heart were confined largely to the auricles.

In two cases the symptoms were entirely neurological. In Case 8 there were limited cardiac changes. In Case 10 there were limited cerebral changes which were not sufficient to explain the course; the extensive myocardial damage offered a much more satisfactory cause.

A febrile reaction was present in every instance. In Case 4, the temperature was elevated only during the period of cardiac failure. In several cases the temperature reached only 100° or 101° F.

A persistent discrepancy between the rate of the pulse and the height of the temperature was present in eight cases. In one (Case 4) it was present only during the last few hours, and in two (Cases 8 and 10) it was absent.

#### SUMMARY AND CONCLUSIONS

Eleven cases of infected thrombi of the heart are reported. In the majority of cases the patients came under observation because of cardiac failure or developed failure as a terminal phenomenon. In all but one case the infection of the heart appeared to be secondary to pneumonia. An embolic process was suggested in many instances. Some may have been lymphogenous in origin. All of the patients had some degree of fever. A discrepancy between the pulse rate and the temperature level was present in all instances in which there were manifest cardiac symptoms.

Bacteriologic investigation of cardiac thrombi offers a field which may lead to clarification of some cases of cardiac failure.

The bacteriologic work was carried out by Miss Sara A. Scudder, bacteriologist of the institution.

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# SYPHILITIC CARDIOVASCULAR DISEASE AND BACTERIAL ENDOCARDITIS

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THIS study was undertaken in order to ascertain the frequency with which syphilitic heart disease and bacterial endocarditis are associated with each other and also the importance of syphilis as a predisposing factor in the development of superimposed bacterial endocarditis. A review of 4,000 consecutive autopsies at the Institute of Pathology of the University Hospitals of Cleveland revealed five cases in which there was a diagnosis of both cardiovascular syphilis and bacterial endocarditis. However, four of these hearts also revealed stigmata of rheumatic fever, and this altered the significance of the syphilis in relation to the bacterial lesion. The results are at variance with several recent reports dealing with coexistent syphilis and bacterial endocarditis.<sup>1-3</sup>

## REPORT OF CASES

CASE 1.—A 55-year-old white man was admitted to the hospital Jan. 6, 1931, and died March 12, 1931. His complaints on admission were shortness of breath and weakness of one year's duration and swelling of the legs of one month's duration. There was a history of a chancre at the age of 20 but no history of rheumatic fever. Physical examination revealed an enlarged heart, systolic and diastolic murmurs over the aortic area, and generalized edema. The blood pressure was 145/55. There were no petechiae or emboli, and the spleen was not palpable. Laboratory examination revealed a moderate anemia, microscopic hematuria, a strongly positive blood Wassermann reaction, and a blood urea nitrogen of 91 mg. per 100 c.c. The patient had a persistent, low-grade fever. No blood cultures were made. The clinical diagnoses were syphilitic heart disease, with aortic insufficiency, chronic glomerulonephritis, and congestive heart failure.

The diagnoses at autopsy were endocarditis lenta involving the aortic and mitral valves; syphilitic aortitis and aortic valvulitis; rheumatic heart disease, with chronic aortic and mitral valvulitis; cardiac hypertrophy and dilatation (730 Gm.); recent infarcts of the spleen; subacute diffuse glomerulonephritis; and chronic passive hyperemia of the viscera. Culture of the heart's blood yielded no growth. Bacterial stain of a vegetation showed Gram-positive cocci.

There was a patchy syphilitic lesion of the root of the aorta, involving especially the regions above the commissures (Fig. 1). The aortic valve showed marked rheumatic disease, i.e., thickening and retraction of the cusps, eversion of the free margins, and fusion of the left-right and right-posterior commissures. Syphilis of

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Fig. 1.—Case 1. Combined syphilitic and rheumatic disease of the aortic valve, with endocarditis lenta, in a 55-year-old white man. There are elevation and widening of the proximal portions of the raphes at commissures A and B. A vegetation is attached to the free margin of the posterior cusp adjacent to commissure B. The anterior mitral leaflet shows ulceration (a) and numerous vegetations.

In photographs of the aortic valve, A represents the left-right commissure; B, the right-posterior commissure; C, the left-posterior commissure; lc, the ostium of the left coronary artery; and rc, the ostium of the right coronary artery.



Fig. 2.—The mitral valve in Case 1. The anterior leaflet shows vegetations on the free margin (a) and adjacent chordae tendineae. Although no gross rheumatic disease is evident, microscopic examination revealed diffuse chronic valvulitis.

the aortic valve could not be diagnosed grossly. However, the proximal portions of the commissural raphe were elevated and widened, suggesting a superimposed syphilitic involvement. The left-posterior commissure showed no change. There was a nodular calcific deposit in the distal portion of the raphe at the left-right commissure, in the left and right cusps adjacent to this raphe, and in the base of the right cusp. Small, friable, grayish-red vegetations were attached to the free margin of the posterior aortic cusp near the right-posterior commissure and to the distal ventricular aspect of the raphe at the left-right commissure. Numerous vegetations were also present on the aortic surface of the anterior mitral leaflet, which showed extensive ulceration, and on the free margin and adjacent chordae tendineae of this leaflet (Fig. 2). There was no gross rheumatic disease of the mitral, tricuspid, or pulmonary valves.

Microscopic sections of the aortic valve through the commissural raphe revealed extension of the syphilitic lesion of the aorta into the ring of the valve, with irregular hyaline thickening and vascularity of the annulus fibrosus. The raphe were the seat of diffuse fibrosis, but vascularity and inflammation were confined largely to the ventricular aspect of the distal and basal portions just above the subaortic angle. Numerous sections of the aortic and mitral valves showed fibrosis, vascularity to the line of closure with capillaries, arterioles, and thick-walled small arteries, and lymphocytic infiltration. These changes involved both the ring and free portion and were most marked on the atrial side of the mitral valve and on the ventricular side of the aortic valve. The tricuspid and pulmonary valves and the left atrium showed no significant change. There were no Aschoff bodies in the myocardium. The vegetations were composed of masses of necrotic fibrinoid material and superficial colonies of bacteria. There were a slight exudation of lymphocytes and polymorphonuclears at the base and also an increase in the number of histiocytes and fibroblasts.

CASE 2.—A 47-year-old Negro was admitted to the hospital Feb. 11, 1933, and died Feb. 21, 1933. His complaints on admission were fever, chills, and pain in the left foot of two months' duration. He gave a history of injury to the left foot in August, 1932. He had a chancre at the age of 32; there was no history of rheumatic fever. On physical examination the heart was enlarged, and there were systolic and diastolic murmurs over the aortic area. The blood pressure was 130/50. The patient had a septic fever, anemia, microscopic hematuria, and conjunctival petechiae. There were no emboli, and the spleen was not palpable. Two blood cultures yielded *Streptococcus alpha*. The clinical diagnoses were streptococcus septicemia, acute bacterial endocarditis, with aortic insufficiency, tertiary syphilis, mild congestive heart failure, and bronchopneumonia.

The diagnoses at autopsy were organizing acute bacterial endocarditis involving the aortic, mitral, and tricuspid valves and the endocardium of the left ventricle; syphilitic aortitis; cardiac hypertrophy and dilatation (410 Gm.); recent infarcts of the right lung, kidneys, and spleen; and chronic passive hyperemia of the viscera. Culture of the heart's blood yielded *Streptococcus alpha*.

There was diffuse syphilis of the root of the aorta, with extension into the sinuses of Valsalva, but no involvement of the aortic valve. No conclusive gross evidence of rheumatic heart disease was present. The aortic, mitral, and tricuspid valves were the seat of bacterial endocarditis. The vegetations were large, grayish-red, and friable, and not firmly adherent to the endocardium. All three aortic cusps were involved extensively and largely destroyed (Fig. 3). Below the aortic valve, vegetations were attached to the membranous portion of the interventricular septum, which was superficially ulcerated, and to the base of the anterior mitral

leaflet. In the latter situation the lesions penetrated the leaflet and projected from its atrial aspect. A single, large, polypoid vegetation was attached to the line of closure of the tricuspid septal leaflet, and small vegetations were present on several adjacent chordae tendineae.



Fig. 3.—Case 2. Combined syphilitic aortitis and acute bacterial endocarditis of the aortic valve in a 47-year-old Negro. The base of the anterior mitral leaflet also shows vegetations.

Numerous microscopic sections of the central and lateral portions of the aortic cusps, and also of the commissural extremities, revealed no evidence of syphilis or rheumatic disease. In some places the syphilitic lesion in the aorta extended as far as the ring of the aortic valve, but the ring itself was not involved. Sections of the posterior mitral leaflet, the anterior and posterior tricuspid leaflets, the pulmonary valve, the ventricles, and the left atrium showed no conclusive evidence of rheumatic heart disease. There was extensive disease of the basal third of the anterior mitral leaflet, involving the myocardial fibrous boundary, the intervalvular fibrosa, and the subvalvular endocardium of the aortic valve. This entire region revealed marked, recent fibrosis, extensive vascularization, and exudation of lymphocytes and monocytes. In the tricuspid septal leaflet there were subacute inflammation and abscess formation in the ring and subvalvular endocardium. However, the free portion of the leaflet revealed no change except slight exudation of polymorphonuclear leucocytes at the base of the vegetations. The vegetations consisted of necrotic, eosinophilic material which contained many polymorphonuclear leucocytes and colonies of bacteria. Some lesions, especially in the aortic mitral leaflet, showed organization at their base.

CASE 3.—A 58-year-old Negro was admitted to the hospital May 10, 1934, and died May 16, 1934. He complained of pain in the chest and fever of two weeks' duration. There was no history of syphilis. He had had three attacks of acute rheumatic fever, the first at the age of 10 years. The heart was enlarged, and a systolic and diastolic murmur was heard over the precordium. The blood pressure was 155/45. There were remittent fever, anemia, microscopic hematuria, conjunctival petechiae, and evidence of embolism of the left foot and arm. The spleen was not palpable. The blood Wassermann was strongly positive (four plus). A Type IV pneumococcus was recovered from the blood stream and from the sputum. The clinical diagnoses were acute bacterial endocarditis of the aortic valve, engrafted on syphilitic valvulitis, pneumococcus septicemia, bronchopneumonia, and congestive heart failure.

The main diagnoses at autopsy were acute bacterial endocarditis involving the aortic and mitral valves and the endocardium of the left ventricle; syphilitic aortitis; rheumatic heart disease, with chronic aortic and mitral valvulitis and chronic endocarditis of the left atrium; cardiac hypertrophy and dilatation (530 Gm.); recent infarcts of the spleen and left kidney; and bronchopneumonia. Culture of a vegetation yielded a Gram-positive diplococcus which was not isolated; culture of the heart's blood showed *Staphylococcus aureus*.

The root of the aorta revealed intimal wrinkling and scarring which were typical of syphilis, but the lesion did not extend into the aortic valve. This valve was the seat of rheumatic disease. The left and posterior cusps were adherent and showed diffuse thickening and retraction adjacent to the commissural raphe. The left-right and the right-posterior commissures were normal. There were thickening and slight nodularity of the left atrial endocardium above the posterior mitral leaflet. The mitral valve showed thickening along the line of closure, but the tricuspid and pulmonary valves were grossly negative.

The right and left aortic cusps were destroyed largely by friable, grayish-red vegetations. These extended from the free margin to the base and down over the endocardium below the right cusp, where there was slight penetration of the membranous portion of the interventricular septum. Vegetations were also attached to several chordae tendineae near the free margin of the anterior mitral leaflet.

The only microscopic sections available were several from the ventricles and one from the aortic valve. The myocardium showed slight perivascular fibrosis, subacute myocarditis, and focal abscesses. The aortic valve was destroyed completely and had been replaced by irregular masses of necrotic fibrin containing numerous polymorphonuclear leucocytes and colonies of bacteria. There was no organization of these lesions.

CASE 4.—A 45-year-old white man was admitted to the hospital Feb. 13, 1935, and died March 11, 1935. On admission he complained of cough, fever, and swelling of the ankles of four weeks' duration. He had a chancre at the age of 20, but there was no history of rheumatic fever. The heart was enlarged, and there were systolic and diastolic murmurs over the aortic area. The blood pressure was 130/80. The patient had fever and microscopic hematuria, but there were no anemia, petechiae, or emboli. The spleen was not palpable. Five blood cultures were negative. The blood and spinal fluid Wassermann reactions were positive. The clinical diagnoses were syphilitic heart disease, with aortic insufficiency, tabes dorsalis, and congestive heart failure.

The diagnoses at autopsy were endocarditis lenta involving the aortic and mitral valves, syphilis of the aorta and of the aortic valve, chronic rheumatic mitral valvulitis, cardiac hypertrophy and dilatation (450 Gm.), tabes dorsalis, chronic passive hyperemia of the viscera, and bronchopneumonia. Cultures of the heart's blood and of a vegetation showed no growth. Bacterial stains of a vegetation revealed Gram-positive cocci.

The root of the aorta revealed a typical syphilitic lesion involving the aortic valve in the region of the right-posterior commissure. At this site the right and posterior cusps were thickened and retracted and the commissure was slightly widened. The rest of the aortic valve showed no significant change. Both mitral leaflets were the seat of marked, diffuse thickening, and there were shortening, thickening, and adhesion of the chordae tendineae. The tricuspid and pulmonary valves and the left atrium were not diseased. Many small, friable, grayish-brown vegetations were attached to the ventricular aspect of the line of closure and mid-portion of all the aortic cusps, and also to the line of closure and free margin of the mitral leaflet and several chordae tendineae below the free margin.

Microscopically, the lateral extremities of the right and posterior aortic cusps adjacent to the right-posterior commissure revealed syphilitic involvement of the ring, with inflammation and scarring. In the free portion the only change was marked hyaline fibrosis. Numerous sections of the lateral and central segments of the cusps showed slight fibrosis, but no vascularity or exudation. In the myocardium there were perivascular fibrosis, subacute inflammation, and several typical Aschoff bodies. The mitral leaflets showed fibrosis, many lymphocytes and plasma cells, and diffuse vascularity with capillaries, arterioles, and thick-walled, small arteries. No significant change was present in the tricuspid or pulmonary valve, or in the left atrium. The vegetations consisted of necrotic fibrin, groups of polymorphonuclear leucocytes, and superficial colonies of bacteria. Slight organization was present at the base.

CASE 5.—A 44-year-old colored woman was admitted to the hospital Dec. 19, 1940, and died Dec. 29, 1940. She complained of shortness of breath of six months' duration. A diagnosis of aortic insufficiency had been made in 1931. There was no history of syphilis. She had had rheumatic fever at the age of 14. Physical examination revealed an enlarged heart, with systolic and diastolic murmurs over the aortic area. The blood pressure was 150/30. The patient showed slight fever, anemia, microscopic hematuria, and a strongly positive blood Wassermann reaction. There were no petechiae or emboli, and the spleen was not palpable. No blood cultures were made. The clinical diagnoses were syphilitic heart disease, with aortic insufficiency. Death was caused by acute pulmonary edema.



Fig. 4.—Case 5. Combined syphilitic and rheumatic disease of the aortic valve, with endocarditis lenta, in a 44-year-old colored woman. There are extensive vegetations in the region of commissure B. The aortic cusps are thickened and retracted, and there is commissural separation. The rheumatic lesion was established microscopically.

The diagnoses at autopsy were endocarditis lenta involving the aortic, mitral, and tricuspid valves and the intima of the root of the aorta; syphilis of the aorta and syphilitic aortic valvulitis, with insufficiency; rheumatic heart disease, with chronic aortic, mitral, and tricuspid valvulitis; cardiac hypertrophy and dilatation (450 Gm.); remote infarct of the left kidney; ascites; edema of the lower extremities; and bronchopneumonia. Culture of the heart's blood showed no growth. Culture of a vegetation on the aortic valve yielded *Streptococcus alpha*.

There was a diffuse syphilitic lesion of the root of the aorta, with extension into the aortic valve. The aortic cusps were thickened and retracted, especially at the commissural extremities, and all three commissures were widened (Fig. 4). Whether

or not there was rheumatic disease of the aortic valve could not be ascertained grossly because of the marked syphilitic lesion. The mitral, tricuspid, and pulmonary valves and the left atrium showed no evidence of rheumatic disease. There were large, friable, grayish-red vegetations on the ventricular aspect of all the aortic cusps, especially the right and posterior cusps. Vegetations were also attached to



Fig. 5.—The mitral valve in Case 5. The anterior leaflet shows a single large vegetation at the line of closure. No conclusive evidence of rheumatic disease is present in the gross, although microscopic section (Fig. 6) revealed typical chronic valvulitis.



Fig. 6.—Case 5. Microscopic section of the posterior mitral leaflet at the line of closure (hematoxylin and eosin,  $\times 130$ ). There are fibrosis, vascularity with arterioles and thick-walled small arteries, and lymphocytic exudate.

the endocardium of the left ventricle below the aortic valve, where they penetrated the membranous portion of the interventricular septum and projected into the right ventricle in the region of the septal anterior commissure. Several vegetations were present on the line of closure of the tricuspid septal leaflet. A single large vegetation was attached to the atrial aspect of the line of closure of the anterior mitral leaflet, and there were smaller lesions on the adjacent chordae tendineae (Fig. 5).

Microscopically, the commissural extremities of the aortic cusps showed a syphilitic lesion of the ring and basal free portion, consisting of irregular hyaline

fibrosis and vascularization with capillaries and arterioles. The central portions of the cusps were not involved by syphilis; however, they showed diffuse change, chiefly in the ring spongiosa and ventricularis layer, consisting of fibrosis, vascularization to the line of closure with various types of vessels, including thick-walled small arteries, and focal lymphocytic exudate. The mitral valve (Fig. 6), and also the tricuspid to a less marked degree, revealed vascularity and chronic inflammation in the ring and free portion. The pulmonary valve and the left atrium showed no significant lesion. In the myocardium there were tiny focal abscesses, subacute inflammation, and suggestive, but not typical, Aschoff bodies. The vegetations consisted of masses of necrotic amorphous material, containing polymorphonuclear leucocytes and superficial colonies of bacteria. There was slight proliferation of fibroblasts at the base. Tiny vegetations, which had not been apparent grossly, were present on the intimal surface of the aorta in the sinus of Valsalva.

#### SUMMARY OF CASES

A summary of the clinical and pathologic data is presented in Tables I and II. Four of the patients were males and one was a female; three were negroes and two were white; and the ages ranged from 44 to 58 years. Three patients gave a history of a primary syphilitic lesion, and two others had a history of acute rheumatic fever. On physical examination all presented the typical signs of aortic regurgitation. The blood Wassermann reaction was positive in all cases. The duration of the illness ranged from three weeks to fourteen months. There were positive blood cultures in two cases.

A clinical diagnosis of syphilitic heart disease was made in four cases because of the history, positive Wassermann reaction, and signs of aortic insufficiency. Evidence of central nervous system syphilis was present in one case. In Case 2 the aortic regurgitation was attributed to bacterial endocarditis. In one instance (Case 5) a diagnosis of syphilitic aortic regurgitation was made nine years prior to the onset of the bacterial lesion. Bacterial endocarditis was diagnosed clinically in only two cases, and both were of the acute type. In two instances (Cases 1 and 5) there were no signs or symptoms indicative of bacterial endocarditis, and therefore the presence of the disease was not suspected during life. The presence of rheumatic heart disease was not detected clinically in any of the cases, either because the lesions were obscured by the syphilis or because they were of a slight and nondeforming nature.

Syphilis of the root of the aorta was present in all cases, and in three instances there was extension into the aortic valve. Unequivocal evidence of rheumatic heart disease was found in four cases, and in one instance (Case 2) there were suggestive, but not conclusive, lesions in the mitral and tricuspid valves. Aschoff bodies were present in the myocardium in one case. A combined syphilitic and rheumatic lesion of the aortic valve was demonstrated in two cases and probably was



TABLE I  
CLINICAL DATA IN CASES OF SYPHILIS, RHEUMATIC FEVER, AND BACTERIAL ENDOCARDITIS\*

| CASE | AGE<br>(YR.) | SEX | RACE  | DURATION<br>OF<br>ILLNESS | HISTORY<br>OF<br>SYPHILIS | HISTORY<br>OF<br>RHEUMATIC<br>FEVER | CARDIAC<br>FINDINGS     | WASSERMANN | BLOOD<br>CULTURES                    | CLINICAL DIAGNOSES   |
|------|--------------|-----|-------|---------------------------|---------------------------|-------------------------------------|-------------------------|------------|--------------------------------------|--|
| 1    | 55           | M.  | White | 14 months                 | Primary<br>lesion         | None                                | Aortic<br>regurgitation | 4 plus     | None made                            | Syphilitic heart disease,<br>with aortic insufficiency   |
| 2    | 47           | M.  | Negro | 9 weeks                   | Primary<br>lesion         | None                                | Aortic<br>regurgitation | 4 plus     | <i>Streptococcus</i><br><i>alpha</i> | Acute bacterial endocarditis<br>of aortic valve, with in-<br>sufficiency; tertiary syph-<br>ilis                                   |
| 3    | 58           | M.  | Negro | 3 weeks                   | None                      | 3 attacks, first<br>at 10 years     | Aortic<br>regurgitation | 4 plus     | Pneumococcus<br>Type IV              | Acute bacterial endocarditis<br>engrafted on syphilitic<br>aortic valvulitis; broncho-<br>pneumonia; pneumo-<br>coccus septicaemia |
| 4    | 45           | M.  | White | 2 months                  | Primary<br>lesion         | None                                | Aortic<br>regurgitation | 4 plus     | Five negative<br>cultures            | Syphilitic heart disease,<br>with aortic insufficiency   |
| 5    | 44           | F.  | Negro | 6.5 months                | None                      | 1 attack at age<br>of 14 years      | Aortic<br>regurgitation | 4 plus     | None made                            | Syphilitic heart disease,<br>with aortic insufficiency   |

\*Although rheumatic fever was not established in Case 2, it is included in the table for convenience.

present in a third (Case 4). The distribution of the bacterial vegetations is shown in Table II. The aortic and mitral valves were involved in every case, and in four instances the mitral lesions may have resulted from apposition with the aortic valve.

TABLE II  
ANATOMIC DISTRIBUTION OF LESIONS IN CASES OF CARDIOVASCULAR SYPHILIS,  
RHEUMATIC HEART DISEASE, AND BACTERIAL ENDOCARDITIS

| CASE | SYPHILIS                       | RHEUMATIC HEART DISEASE               |  | BACTERIAL ENDOCARDITIS  |
|------|--------------------------------|---------------------------------------|--|---|
|      |                                | GROSS LESIONS                         | MICROSCOPIC LESIONS                            |   |
| 1    | Root of aorta and aortic valve | Aortic valve                          | Aortic and mitral valves                       | Aortic and mitral valves  |
| 2    | Root of aorta                  | None                                  | None   | Aortic, mitral, and tricuspid valves; endocardium of left ventricle |
| 3    | Root of aorta                  | Aortic and mitral valves; left atrium | Sections not available                         | Aortic and mitral valves; endocardium of left ventricle             |
| 4    | Root of aorta and aortic valve | Mitral valve                          | Mitral valve; Aschoff bodies in left ventricle | Aortic and mitral valves  |
| 5    | Root of aorta and aortic valve | None                                  | Aortic, mitral, and tricuspid valves           | Aortic, mitral, and tricuspid valves; intima of root of aorta       |

#### COMMENT

Table III presents data pertaining to the incidence of combined syphilitic heart disease and bacterial endocarditis in autopsy material. The total number of cases of bacterial endocarditis and also the number among these in which there were syphilitic aortitis and syphilis of the aorta and aortic valve are given. The figures generally indicate that association of the two diseases is infrequent or rare, but this is contrary to the experience of Braunstein and Townsend<sup>1</sup> and Wright and Zeek,<sup>2</sup> who found a much higher incidence. Apparently the combination of bacterial endocarditis and syphilitic aortitis alone occurs with approximately the same frequency as bacterial endocarditis and syphilitic aortitis with involvement of the aortic valve.

It generally is agreed that syphilitic aortitis alone does not predispose the aortic valve to the development of bacterial endocarditis.<sup>2-4, 7</sup> The association of a syphilitic lesion confined to the root of the aorta and bacterial vegetations of the aortic valve is in all probability merely coincidental. In such cases there is either an underlying nonsyphilitic valvulitis, chiefly rheumatic, or the bacterial lesion, especially if it is acute, is superimposed on a normal aortic valve. The latter probably holds for Case 2 of the present study. In cases of combined syphilitic

disease and bacterial endocarditis of the aortic valve, syphilis can be considered a predisposing factor only after excluding rheumatic heart disease, for the latter is the usual precursor of bacterial endocarditis. This requires careful examination of both the aortic valve and the rest of the heart for rheumatic stigmata.

TABLE III  
INCIDENCE OF COMBINED SYPHILITIC HEART DISEASE AND BACTERIAL  
ENDOCARDITIS IN AUTOPSY MATERIAL

| YEAR | INSTITUTION   | OBSERVER                                     | NO. OF<br>CASES OF<br>BACTERIAL<br>ENDO-<br>CARDITIS* | CASES OF<br>SYPHILIS OF<br>AORTA† |      | CASES OF<br>SYPHILIS OF<br>AORTA AND<br>AORTIC VALVE |      |
|------|---|--|---|-----------------------------------|------|--|------|
|      |   |  |   | NO.                               | %    | NO.  | %    |
| 1926 | Johns Hopkins   | Thayer <sup>4</sup>                          | 130   |                                   |      | 2  | 1.5  |
| 1937 | Mt. Sinai   | Gross and<br>Fried <sup>5</sup>              | 70  |                                   |      | 1  | 1.4  |
| 1938 | Los Angeles<br>County   | Martin and<br>Adams <sup>6</sup>             | 157   | 5                                 | 3.2  | 2  | 1.3  |
| 1940 | Baltimore City  | Braunstein<br>and Town-<br>send <sup>1</sup> | 58  |                                   |      | 9  | 15.5 |
| 1940 | Cincinnati General  | Wright and<br>Zeek <sup>2</sup>              | 84  | 18                                | 21.4 | 10   | 12.0 |
| 1940 | Michael Reese and<br>Cook County  | Rosenberg <sup>3</sup>                       | 273   | 19                                | 7.0  | 7  | 2.6  |
| 1942 | Institute of<br>Pathology, Uni-<br>versity Hos-<br>pitals of Cleve-<br>land | Koletsky                                     | 80  | 5                                 | 6.3  | 3  | 3.8  |

\*The figures represent the total number of cases of bacterial endocarditis, not merely those of involvement of the aortic valve. Both subacute and acute forms are included.

†The figures represent the total number of cases of syphilitic aortitis, both with and without involvement of the aortic valve.

A rheumatic lesion of the aortic valve may be obscured in the presence of syphilis and hence may be difficult or impossible to detect grossly. This is especially true when the valve is the seat of extensive syphilis, with thickening and commissural separation of cusps and only minimal rheumatic disease. The identification of a well-developed rheumatic lesion is comparatively simple when the syphilis is slight. Submarginal adhesions of adjacent cusps, or fusion, with the formation of a commissural raphe, are presumptive evidence of rheumatic heart disease, for syphilis rarely, if ever, produces such deformities. Other indications of the presence of rheumatic heart disease are marked thickening and retraction in the central and lateral portions of the cusps, with only slight involvement of the commissural extremities.

A microscopic diagnosis of rheumatic involvement of the aortic valve often can be established in the presence of syphilis because the two lesions differ in type and distribution.<sup>9</sup> The syphilitic change<sup>8, 9</sup> is

confined largely to the commissural extremities of the cusps, and, since these are involved by direct extension from the aorta, the inflammation and scarring are marked in the ring and base of the cusp and diminish as the free margin is approached. The midportions of the cusps may be the seat of fibrosis, but, even when the lesion is extensive, they show no vascularity or significant exudate. Direct extension of syphilis from the aorta into the central portions of the cusps, i.e., the so-called ascending type of lesion, is uncommon, and, when present, the inflammation is largely limited to the ring. In contrast, well-developed rheumatic fever produces a more or less diffuse valvulitis and can thus be recognized by characteristic inflammatory changes in the central and lateral regions of the cusps, where there is no significant overlapping with syphilis. Vascularization, exudation, and fibrosis are present both in the ring and free portion of the cusps, chiefly in the ventricularis layer, and may extend to the line of closure. The commissural raphe of rheumatic fever is distinctive and readily identified microscopically. There is diffuse hyaline fibrosis, but vascularity and inflammation usually are confined to the distal and basal portion of the ridge, just above the sub-aortic angle.

In some instances of slight rheumatic involvement of the aortic valve, however, positive identification of the lesion is difficult. The microscopic observations in such cases are often equivocal, especially with respect to the presence of significant vascularity and fibrosis in the free portions of the cusps. The diagnosis of rheumatic heart disease then depends upon the recognition of stigmata of rheumatic fever elsewhere in the heart. These are especially common in the mitral and tricuspid valves, where they are easily recognized. The gross stigmata include thickening of the mitral, tricuspid, and pulmonary valves, particularly along the line of closure and free margin; thickening, shortening, and adhesion of the chordae tendineae; irregular thickening and wrinkling of the left atrial endocardium above the posterior mitral leaflet; and fibrous pericardial adhesions, especially in the atrioventricular sulci. Characteristic microscopic lesions consist of vascularity, fibrosis, and exudate in the ring and free portions of the mitral, tricuspid, and pulmonary valves; vascularity and reduplication of the elastica of the endocardium of the left atrium; and Aschoff bodies in the myocardium. These stigmata cannot be confused with syphilis, for the latter is practically confined to the aortic valve. Whether the rare cases<sup>10, 11</sup> of alleged syphilitic stricture of the mitral valve are authentic is open to doubt. Very rarely the syphilitic lesion of the aortic valve spreads down into the membranous portion of the interventricular septum and anterior mitral leaflet. Three such cases have been described.<sup>12, 13</sup> In all of these, however, there was gummatous necrosis of the anterior mitral leaflet, and this, together with the demonstration of extension from the aortic valve,

would readily distinguish the lesion from that caused by rheumatic fever.

There were three cases of syphilitic aortic valvulitis in this study; a rheumatic lesion of the aortic valve was demonstrated grossly in one, and microscopically in another. There were two additional cases of syphilitic aortitis, and gross rheumatic disease of the aortic valve was observed in one. However, unequivocal rheumatic stigmata were identified in other parts of the heart in four cases, and in two instances the lesions were entirely microscopic. This indicates the importance of complete microscopic study when no conclusive evidence of rheumatic disease is present grossly. Blocks should be made according to the method of Gross, Antopol, and Sacks.<sup>14</sup> Even multiple sections of the valves, especially the mitral and tricuspid, are of value in some cases, for the first section may be equivocal or negative, whereas, in additional sections, the signs of inflammation are plainly evident.

Until 1940, only a small number of cases of coexisting syphilitic aortic valvulitis and bacterial endocarditis had been reported. Of these, Braunstein and Townsend,<sup>1</sup> Wright and Zeek,<sup>2</sup> and Rosenberg<sup>3</sup> accept, as authentic, eleven, six, and nine cases, respectively. A summary of the latter has appeared in their papers<sup>1-3</sup> and need not be presented here. However, a review of the cases reveals that in most instances the diagnoses were based on gross observation; microscopic study was entirely lacking or inadequate. This would result in the recognition of pronounced rheumatic lesions, but slight disease may have been overlooked. Moreover, in some instances, the mitral and tricuspid valves showed vegetations which did not appear to be the result of apposition with the aortic valve, and these may have been engrafted on rheumatic disease. Since rheumatic heart disease was not satisfactorily excluded, very few, if any, of these cases should be accepted as authentic instances of bacterial endocarditis superimposed on a syphilitic lesion.

In 1940 there were several reports dealing with coexisting syphilis and bacterial endocarditis of the aortic valve, and all presented similar conclusions. Wright and Zeek<sup>2</sup> described five cases, which constituted 7 per cent of sixty-eight autopsy cases of syphilitic aortic valvulitis at the Cincinnati General Hospital and concluded that syphilis of the aortic valve was an important precursor of bacterial endocarditis. Braunstein and Townsend<sup>1</sup> reported nine cases, which represented 3.3 per cent of 267 cases of syphilitic aortic valvulitis from among 4,921 consecutive autopsies at the Baltimore City Hospital. This incidence was held to indicate that the combination of bacterial endocarditis and syphilitic aortic valvulitis was more common than is generally stated. A similar conclusion was reached by Rosenberg,<sup>3</sup> who described seven autopsy cases of syphilis and bacterial endocarditis of the aortic valve from the Michael Reese and Cook County Hospitals.

In two of these reports<sup>2, 3</sup> the authors stated that the presence of rheumatic lesions was excluded in their cases. However, no mention was made of any investigation of the aortic valve to rule out an obscure rheumatic lesion, or of complete microscopic examination of other valves for rheumatic stigmata. The conclusion that syphilitic aortic valvulitis not infrequently acts as a precursor of bacterial endocarditis is at variance with the older belief<sup>4, 15</sup> that this combination is extremely rare. In our experience the association of cardiovascular syphilis and bacterial endocarditis has been infrequent, rather than rare, and largely confined to hearts which were the seat of rheumatic disease. There were rheumatic stigmata in five of the ten cases of syphilitic aortic valvulitis and bacterial endocarditis studied by Wright and Zeek.<sup>2</sup> It is clear that hearts with a combined syphilitic and bacterial lesion may harbor rheumatic disease and that the latter, especially if it is slight, will be overlooked when the examination of the heart is incomplete.

Only scant data are available on the frequency of combined cardiovascular syphilis and rheumatic heart disease. Among 1,031 autopsies at City Hospital, Welfare Island, Lisa and Chandlee<sup>16</sup> encountered seventy-one cases of syphilitic heart disease, exclusive of aneurysm, and in eight, or 12 per cent, of these, there were also rheumatic lesions. Swanson<sup>17</sup> found four instances (7 per cent) of syphilitic aortitis associated with rheumatic heart disease among fifty-seven cases of cardiovascular syphilis of all types in 1,841 autopsies at the Vanderbilt Hospital. However, very few cases of combined syphilitic and rheumatic disease of the aortic valve, established by autopsy, have been reported. There was one in the group described by Lisa and Chandlee,<sup>16</sup> and Sager and Sohval<sup>9</sup> reported three cases in 1934. The figures on combined syphilitic and rheumatic heart disease at the Institute of Pathology of the University Hospitals of Cleveland are of interest. Among 4,000 consecutive autopsies from May, 1930, to May, 1941, there were 135 cases of cardiovascular syphilis, and in twenty-four, or 18 per cent, of these, a diagnosis of rheumatic heart disease was also made. Over the same period, there were 475 cases of rheumatic heart disease and eighty cases of bacterial endocarditis. In four cases there was combined syphilitic and rheumatic disease of the aortic valve. Of the twenty-three hearts which were the seat of both syphilis and rheumatic fever, four, described in this paper, also revealed evidence of bacterial endocarditis.

That bacterial endocarditis is engrafted with far greater frequency on rheumatic than on syphilitic lesions is an established fact. The reasons for this have been largely speculative. The difference in the behavior of these lesions toward bacterial endocarditis is too great to be explained merely by a difference in incidence of cardiovascular syphilis and rheumatic heart disease in various localities.<sup>2</sup> Nor is the suggestion tenable that the rare association of syphilis and bacterial endocarditis is due to the fact that the latter is essentially a disease of younger persons,

whereas cardiovascular syphilis affects an older group.<sup>18</sup> Several morphologic explanations have been offered. One is that the rheumatic valve has greater vascularity than the syphilitic and is thus more likely to become the seat of bacterial invasion. This concept depends upon the theory of embolic origin of endocarditis, which appears not to be generally applicable.<sup>5, 19, 20</sup> Moreover, bacterial endocarditis is frequently superimposed on slight or mild rheumatic lesions which are poorly vascularized. Saphir and Wile<sup>21</sup> suggest that in syphilis the excursion of the aortic cusps is limited, so that only a small area for the settling of bacteria is available. In nonsyphilitic valvulitis, on the other hand, shortening of the cusps in their longitudinal diameter and adhesions at the commissures provide larger than normal areas for bacterial implantation. At present most observers believe that bacterial endocarditis arises chiefly as a surface infection of valves whose damaged endocardium provides an anchoring ground for bacteria.<sup>5, 19, 20</sup> Suitable endocardial changes of degenerative, inflammatory, and thrombotic types are more frequent in rheumatic fever than in syphilis. For example, Grant, Wood, and Jones<sup>19</sup> found that platelet thrombi, which provide a nidus for localization and growth of bacteria, are common in rheumatic valvular disease and infrequent in syphilis.

#### SUMMARY AND CONCLUSIONS

Among 4,000 consecutive autopsies at the Institute of Pathology of the University Hospitals of Cleveland there were five cases of combined syphilitic heart disease and bacterial endocarditis. In two there was syphilitic aortitis alone, and in three there was also involvement of the aortic valve. In no case could significance be attached to the syphilitic lesion as a precursor of bacterial endocarditis. Stigmata of rheumatic fever were demonstrated unequivocally in four cases, and in at least two of these there was a combined syphilitic and rheumatic lesion of the aortic valve. In the fifth case the syphilis was confined to the root of the aorta, and the acute bacterial endocarditis was apparently superimposed on a normal aortic valve. These observations lend no support to the belief that syphilis is a significant predisposing factor in the development of bacterial endocarditis. Hearts with lesions of both syphilis and bacterial endocarditis should be subjected to thorough examination for stigmata of rheumatic fever.

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# LUMBAR SYMPATHECTOMY IN THE TREATMENT OF INTERMITTENT CLAUDICATION

## SELECTION OF CASES BY CLAUDICATION TEST WITH LUMBAR PARAVERTEBRAL PROCAINE INJECTION

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**I**NTERMITTENT claudication is caused by the pain which develops in working muscles in the absence of an adequate circulation. This condition is frequently encountered in patients with arterial occlusion and may be incapacitating. Two theories have been advanced to explain the reduction in circulation: first, that the diminished blood flow is caused by spasm of the blood vessels supplying the muscles; second, that the organic obstruction of the arteries prevents adequate circulation. Both theories maintain, however, that the pain which causes intermittent claudication ultimately derives from a reduction in blood flow through muscles. For a discussion of the mechanism of the pain associated with intermittent claudication, reference is made to the work of Lewis, Pickering, and Rothschild,<sup>1</sup> and Veal and McFetridge.<sup>2</sup>

In the treatment of intermittent claudication, lumbar sympathectomy has been considered ineffective as a means of increasing the blood supply to the muscles of the leg. Homans,<sup>3</sup> in his recent monograph on peripheral vascular disease, stated: "As a cure for intermittent limp, lumbar sympathectomy is not recommended." Landis and Montgomery<sup>4</sup> believed that intermittent claudication was "not affected" by sympathectomy. On the other hand, the following observers have reported cases in which there was considerable relief from claudication after excision or paralysis of the lumbar sympathetic nerves: Brown,<sup>5</sup> Flathow,<sup>6</sup> Morton and Scott,<sup>7</sup> Reichert,<sup>8</sup> Telford,<sup>9</sup> Harris,<sup>10</sup> White,<sup>11</sup> Davis,<sup>12</sup> and Pearl.<sup>13</sup> The improvement consisted of relief of pain and an increase in the "walking distance." No objective evidence that there is an increase in the blood supply to the muscles after sympathectomy has been presented. On the other hand, physiologic observations by Grant and Pearson,<sup>14</sup> Holling,<sup>15</sup> Kunkel, Stead, and Weiss,<sup>16</sup> and Abram-

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son and Ferris<sup>17</sup> have shown in normal human subjects that the blood flow through muscle is actually increased by sympathetic stimulation.

It was therefore felt that some objective method of estimating the severity of intermittent claudication should be used in a study of the benefits to be obtained from paralysis of the vasoconstrictor nerves. Such an objective method is furnished by the claudication test of Hitzrot, Naide, and Landis.<sup>18</sup>

White<sup>19</sup> was the first to suggest blocking the lumbar sympathetic nerves with procaine as a diagnostic procedure. Flothow<sup>6</sup> extended its use, and Reichert<sup>8</sup> actually employed it to evaluate the probable benefits to be derived from prolonged paralysis of the sympathetics with alcohol. Pearl<sup>13</sup> more recently has found it useful in his studies on claudication.

In this study we have measured the severity of intermittent claudication in twelve patients with obliterative vascular disease of the lower extremities, both before and after blocking the lumbar sympathetic ganglia with procaine. The results of the tests, as well as the effects of the subsequent sympathectomies on six of the patients, form the basis for the present communication.

The hypothesis which guided us in the selection of tests, in the interpretation of symptoms, and in planning treatment in the various cases may be stated as follows: In some cases of arterial occlusive disease there is apparently also an element of abnormal vasoconstriction which is superimposed upon the underlying condition and aggravates the circulatory deficiency. The mechanism by which the vasoconstriction aggravates the symptoms of arterial disease will be discussed later. Clinical signs which are interpreted as indicating abnormal vasoconstriction are (1) cyanosis of the feet, (2) increased sweating, and (3) constriction of the superficial veins of the feet and legs when the patients are subjected to the emotional stimulation of examination. Patients who present evidence of abnormal vasoconstriction and show improvement after lumbar paravertebral procaine injection may, we believe, be benefited by lumbar sympathectomy.

#### METHODS

*1. Claudication Test.*—The ability of the calf muscles to contract was studied by means of the claudication test described by Hitzrot, Naide, and Landis.<sup>18</sup> The amount of work which can be performed has been shown to depend upon the efficiency of the circulation. By this method, the muscles of the calf are stimulated at regular intervals by means of electrodes placed on the calf of the leg. Extension of the foot against a spring resistance is measured on a kymograph. The current is adjusted in such a way as to give good contraction of the muscles. Between 2.2 and 3.8 amperes were found to be necessary. The same strength of current was used before and after paravertebral injection on all except one of the patients. We chose to use stimuli at the rate of one every two seconds for two minutes. The patients were then given one minute of rest, and the calf was

TABLE I

| CASE | INITIALS | SEX | AGE<br>(YR.) | DIAGNOSIS                                | MOST DISTAL<br>PULSES<br>PRESENT              | CALCIFI-<br>CATION<br>OF<br>ARTERIES<br>OF LEGS | WALKING DISTANCE    |                    | CLAUDICATION<br>TEST     |                         | MAXI-<br>MUM<br>TEMP-<br>ERATURE<br>OF TOES<br>AFTER<br>INJEC-<br>TION | GANGLIA<br>REMOVED<br>AT<br>OPERATION   | WALKING<br>DISTANCE<br>AFTER<br>LUMBAR<br>SYMPA-<br>THECTOMY |
|------|----------|-----|--------------|--|---|---|---------------------|--------------------|--------------------------|-------------------------|--|---|--|
|      |          |     |              |  |   |   | BEFORE<br>INJECTION | AFTER<br>INJECTION | BEFORE<br>INJEC-<br>TION | AFTER<br>INJEC-<br>TION |  |   |  |
| 1    | H. T.    | M   | 67           | Arteriosclerosis and<br>vasoconstriction | Right and left<br>femorals                    | +   | 1 block             | 2½ blocks          | 3.9                      | 3.6                     | 28.5   | Right<br>L 2, 3, 4<br>Left<br>L 2, 3, 4 | 15 blocks  |
| 2    | H. McC.  | M   | 41           | Vasoconstriction and<br>obliteration     | Right femoral<br>and left<br>dorsalis pedis   | 0   | 100 yards           | 500 yards          | 21.0                     | 17.0                    | 30.1   | Left<br>L 1, 2, 3                       | 2 blocks.<br>Limited<br>by angina<br>pectoris                |
| 3    | T. D.    | M   | 46           | Vasoconstriction and<br>obliteration     | Right dorsalis<br>pedis and left<br>popliteal | +   | 1 block             | 4 blocks           | 11.5                     | 15.9                    | 33.1   | Right<br>L 1, 2, 3<br>Left<br>L 1, 2, 3 | Unlimited  |
| 4    | J. L.    | M   | 65           | Vasoconstriction and<br>obliteration     | Right posterior<br>tibial and left<br>femoral | 0   | 40 yards            | 150 yards          | 8.2                      | 6.5                     | 32.2   |   |  |

|    |       |   |    |   |  |   |                     |                     |      |      |      |                              |
|----|-------|---|----|---|--|---|---------------------|---------------------|------|------|------|------------------------------|
| 5  | J. C. | M | 33 | Thromboangiitis obliterans and vasoconstriction   | Right femoral, left dorsalis pedis, and posterior tibial                                     | 0 | 1 block             | 1 block             | 6.8  | 7.5  | 29.1 |                              |
| 6  | F. D. | F | 52 | Arteriosclerosis                                  | No pulses palpable   |   | $\frac{1}{2}$ block | $\frac{1}{2}$ block | 5.8  |      | 29.5 |                              |
| 7  | L. P. | F | 40 | Diabetes peripheral neuritis and vasoconstriction | Right and left posterior tibials   |   | 2 blocks            | 2 blocks            | 2.0  | 1.0  | 31.4 |                              |
| 8  | A. S. | M | 37 | Thromboangiitis obliterans and vasoconstriction   | Right and left femorals  |   | 1 block             | 4 blocks            | 11.5 | 12.4 | 30.1 | Right L 1, 2, 3<br>8 blocks  |
| 9  | A. N. | M | 32 | Thromboangiitis obliterans and vasoconstriction   | Right femoral and left posterior tibial  |   | 1 block             | 4 blocks            | 9.0  | 14.1 | 30.6 | Right L 1, 2<br>8 blocks     |
| 10 | L. T. | M | 42 | Thromboangiitis obliterans and vasoconstriction   | Right dorsalis pedis and left femoral  | 0 | 3 blocks            | 3 blocks            | 10.7 | 17.2 | 30.8 |                              |
| 11 | C. K. | M | 59 | Vasokonstriction and obliteration                 | Right posterior tibial and left femoral  | 0 | 2 flights of stairs | 5 flights of stairs | 11.0 | 14.7 | 33.2 |                              |
| 12 | A. M. | M | 60 | Vasokonstriction                                  | Right dorsalis pedis, right posterior tibial, left dorsalis pedis, and left posterior tibial | 0 | 2 blocks            | 8 blocks            | 10.0 | 14.0 | 32.2 | Right L 1, 2, 3<br>Unlimited |

stimulated once every second for two minutes. The time of onset of the pain was noted, and, for purposes of comparison (Table I), the average amplitude of contraction during the last ten seconds was taken.

2. *Skin Temperature.*—The skin temperature of the toes was measured by means of a thermocouple connected with a galvanometer. For purposes of record (Table I), the highest skin temperature which was observed after paravertebral procaine block was used.

3. *Paravertebral Block.*—With the patient lying on the normal side, three or four 22 gauge needles, 4 inches long, were inserted opposite the spinous processes of the lower thoracic and upper lumbar vertebrae at a distance of 4 to 6 cm. from the midline. The paths of the needles were infiltrated with a 1 per cent procaine solution which contained adrenalin (three drops of a 1:1,000 solution of adrenalin chloride to the ounce). At a distance of 3 cm. below the transverse processes in the lower thoracic, and 4 cm. in the lumbar, region, 5 c.c. of a 2 per cent procaine solution, with adrenalin, were injected after ascertaining that the tip of the needle was not in a blood vessel, in the pleura, or in the subarachnoid space. Within five to ten minutes, signs of sympathetic paralysis became evident, as shown by (a) dilatation of the superficial veins, (b) improvement in the color of the skin of the leg and foot, (c) absence of sweating, and (d) a rise in skin temperature of the toes of the injected side. When the skin temperature of the toes had reached a stationary level, and when other signs of sympathetic paralysis were present, the patient was placed in the dorsal position, and the claudication test was repeated, using the same strength of current and the same sequence of stimulation.

4. *Walking Distance.*—At the conclusion of the second claudication test the patient was allowed to sit up and then to walk at his customary pace. He was told to stop when the pain became so severe that he normally would have stopped walking.

5. *Precautions.*—The retroperitoneal and retropleural tissues are vascular, and absorption from these places takes place rapidly, possibly by way of the prevertebral veins described by Batson.<sup>20</sup> Several severe reactions were observed. In order to prevent the occurrence of reactions, 1.5 grains of sodium amytal were usually given before the test, and the procaine was injected *slowly*. Psoas weakness was produced occasionally by diffusion of the procaine through the substance of the muscle. This complication followed injections into the third and fourth paravertebral ganglia more frequently than injection into the upper lumbar and lower thoracic ganglia. This weakness was detected when the patient was allowed to sit up at the conclusion of the second claudication test.

6. *Operations.*—The extraperitoneal approach to the lumbar sympathetic ganglia was employed in all of the sympathectomies. This approach was first described by Royle,<sup>21</sup> in 1924. Flothow<sup>22</sup> suggested a muscle-splitting incision in 1935, and this operation was modified by Pearl,<sup>23</sup> in 1937. The aim of the sympathectomy in their cases was to relieve abnormal vasoconstriction in the feet. Full vasodilatation in this region is achieved by resection of the second, third, and fourth lumbar ganglia. Sweating and other evidences of sympathetic activity, however, generally persist above the ankle after this operation. In one of our earlier cases, even though 6.5 inches of the lumbar sympathetic chain were removed, sweating was still present down to the ankle on the medial side of the leg. We accordingly adopted Harris'<sup>10</sup> technique, and made a transverse subcostal incision. Particular efforts were made to extract the first lumbar ganglion from the substance of the diaphragm. Since then, in all of our patients, sweating has been absent below the knee.

## RESULTS

All but one of the patients who were selected for study (Table I) presented evidence of abnormal vasoconstriction, as shown by cyanosis

of the feet, contracted veins (Fig. 1), and sweating under the emotional tension of examination. Ten of the patients showed either subjective or objective improvement after paravertebral procaine block. Fig. 2 shows the record of the claudication test which was done on one of these patients before and after the injection.



Fig. 1.—Infrared photograph of the feet (to show the prominence of the veins on the sympathectomized side. Patient A. M. (Table I, Case 12.)

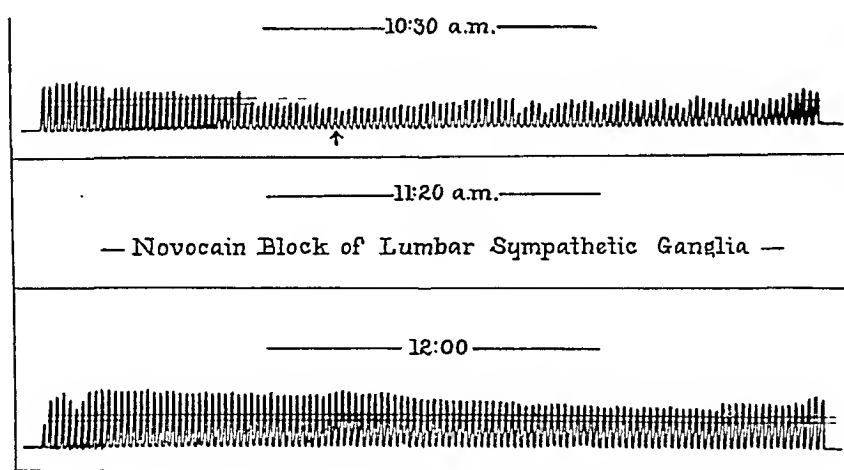


Fig. 2.—Claudication test before and after paravertebral injection of procaine in region of right lumbar sympathetic ganglia (first to fourth lumbar). Patient A. N. (Table I, Case 9.)

One patient with arteriosclerosis, and another with diabetes and peripheral neuritis, showed no improvement, as estimated either by the claudication test or the "walking distance" after the injection.

The temperature of the toes of all the patients who were tested showed a rise when the vasoconstrictor tone was removed. An example of the rise in skin temperature is shown in Fig. 3.

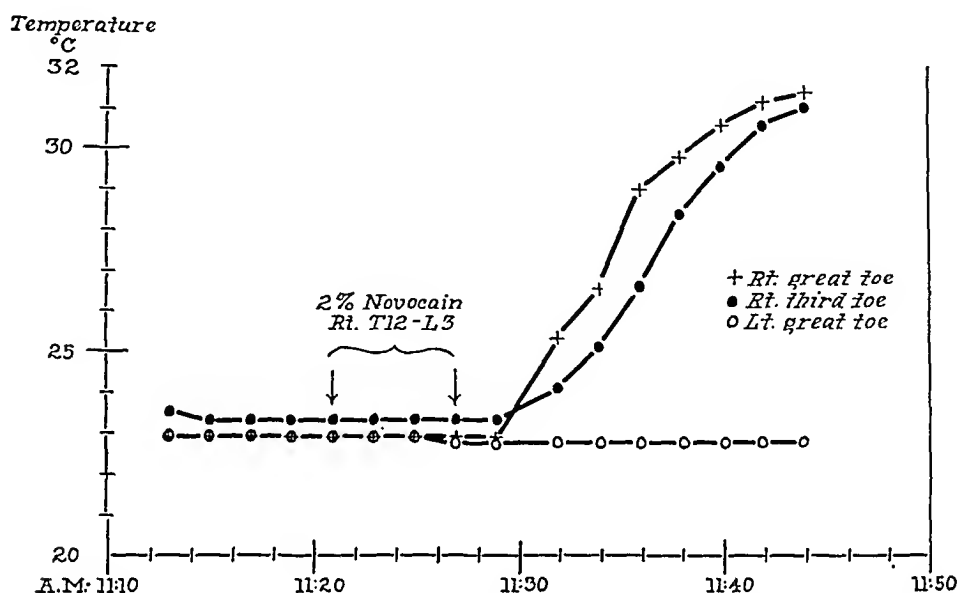


Fig. 3.—Increase in temperature of toes after paravertebral injection of right lumbar sympathetic ganglia. Patient A. N. (Table I, Case 9.)

Six of the ten patients who showed improvement in their ability to walk after paravertebral procaine block were subjected to lumbar sympathectomy, and in two of these cases a bilateral lumbar sympathectomy was performed. In all except one patient, the first, second, and third lumbar ganglia, with the intervening chain, were removed. In one patient with coexistent hypertension, the major and minor splanchnic nerves were also resected. All of the patients recovered from their operations without complications. Immediate and increasing lessening of the intermittent claudication was noted in five of the six patients on whom lumbar sympathectomy was performed.

#### DISCUSSION

Improvement in the ability of the calf muscles to perform work after paralysis of the vasoconstrictor nerves was demonstrated in seven patients. By means of the claudication test, we have, therefore, been able to obtain objective evidence which substantiates the hypothesis that vasoconstriction aggravates the circulatory defect produced by organic arterial obstruction.

The temporary relief from claudication after paravertebral procaine block and the persistent relief after lumbar sympathectomy confirm

the observations of many others who have studied the influence of sympathetic paralysis upon this condition. Our studies, like theirs, however, do not appear to be in harmony with the physiologic evidence that sympathetic stimulation influences blood flow through muscle. Hoskins, Gunning, and Berry<sup>24</sup> were the first to show in the experimental animal that sympathetic stimulation, although it caused vasoconstriction in the skin, produced vasodilatation in muscle. Recent work on man by Grant and Pearson,<sup>14</sup> Holling,<sup>15</sup> Kunkel, Stead, and Weiss,<sup>16</sup> and Abramson and Ferris<sup>17</sup> showed that the blood flow through resting human muscle was increased by sympathetic stimulation or by the intravenous injections of adrenalin. In an effort to harmonize our results with these physiologic observations, various factors will be considered.

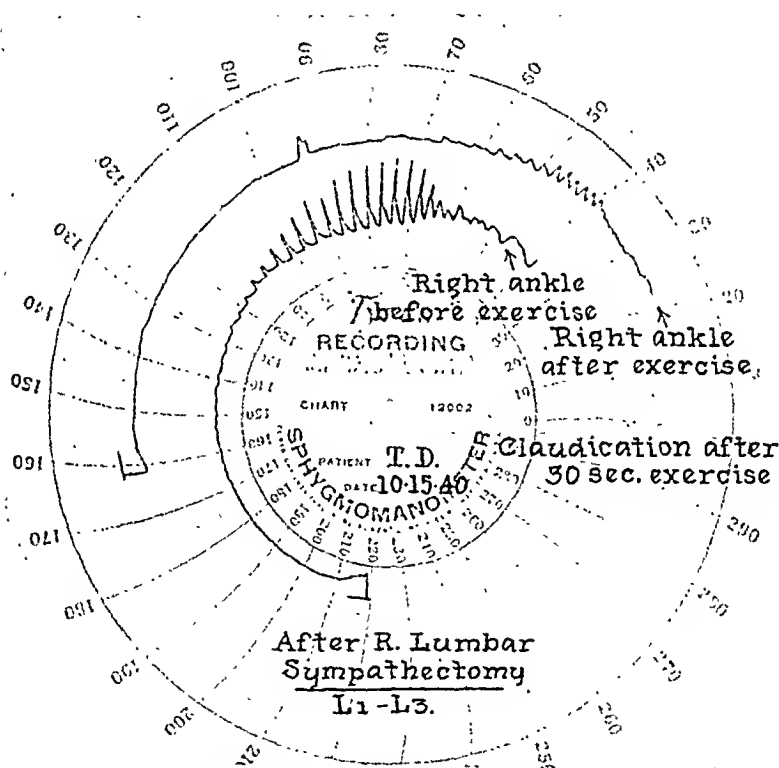


Fig. 4.—Oscillations at the ankle before and after the production of intermittent claudication in a sympathectomized limb. The oscillations just below the knee, but above the calf, were increased after the exercise. Patient T. D. (Table I, Case 3.)

It has been suggested that sympathectomy might interfere with the perception of pain from the blood vessels of the muscles (Leriche<sup>25</sup>). This explanation does not seem likely because the typical pain which induces intermittent claudication was produced in all of our patients, even after sympathectomy, by extending the period of exercise.

Another possibility is the fact that the blood vessels in all of our patients were abnormal, and might have gone into spasm under the ex-



perimental conditions. Pearl<sup>13</sup> has called attention to the clinical signs of vasospasm in the foot and ankle which were associated with the production of intermittent claudication in his cases. He has, in fact, suggested the term "angiospastic claudication" for this condition. He found that the dorsalis pedis pulse disappeared and the foot became blanched when claudication was produced by exercise, even though the pulse had been present and the foot was initially of good color. His observations appear to differ from those of Lewis, Pickering, and Rothseild<sup>1</sup> and Veal and McFetridge<sup>2</sup> on the behavior of the muscle vessels during the pain which causes intermittent claudication. These investigators found that during muscular activity associated with intermittent claudication there was actually an increase in the caliber of the muscle blood vessels, as shown both by blood flow studies and by arteriography. An explanation for Pearl's observations may be that the blood vessels of the calf were wide open as a result of the increased demand of muscular metabolism. In one of our patients, even though the leg was demonstrably sympathectomized below the knee, and, presumably, the ability of the vessels to go into spasm was lost, the foot became pale, the pulses diminished, and the oscillations at the ankle decreased after extended exercise (Fig. 4), whereas the oscillations just below the knee, but proximal to the calf, were actually increased. With the diversion of the available circulation into the dilated blood vessels of the calf, the blood flow to the foot and ankle and the pulsations of the vessels in this region were decreased.

A possible explanation for the beneficial effect of sympathectomy on intermittent claudication is suggested by the ingenious experiments of Roome,<sup>26</sup> who studied the effect of intra-arterial injections of adrenalin on the blood flow through muscle in the anesthetized dog. It is well known from the work of other investigators that a variable reaction is obtained—sometimes dilatation, sometimes constriction—when adrenalin is injected intra-arterially or intravenously. Roome found that the vascular reaction of muscle blood vessels to adrenalin was diphasic. By analyzing the time relationship of the vasomotor response in relation to the rate of flow, he came to the conclusion that the action of adrenalin, when injected intra-arterially, was to constrict the arteries and arterioles of the muscle, but at the same time to dilate the capillaries. The ultimate result on the blood flow depended upon the time at which the adrenalin came into contact with these vessels. With this concept in mind, it is possible to harmonize the reports on the influence of sympathetic stimulation on muscle blood flow with the beneficial results of sympathectomy in the treatment of intermittent claudication. It is quite probable that sympathetic stimulation dilates the muscle capillaries, but, at the same time, especially in patients with abnormal vasoconstriction, it probably constricts the arterioles and the arteries to such a degree as to interfere with the delivery of blood to those capillaries.

After the removal of arteriolar vasoconstrictor tone by sympathectomy, the maximum flow of blood allowed by the obstructed arteries is then available for capillary distribution.

There were two patients in this series (Cases 5 and 10) who showed evidence of objective improvement by the claudication test, and yet obtained no subjective relief after lumbar sympathetic block. Both of these patients were suffering from thromboangiitis obliterans, and it was our feeling that they probably had occlusion of the blood vessels supplying localized areas in the muscles and that it was the ischemia in these areas which was producing the symptoms. Even though paralysis of the vasoconstrictors brought about an increase in blood flow to the calf as a whole and resulted in an increase in the ability to perform work, the ischemia of the localized area was presumably not relieved, so that the symptoms persisted. Sympathectomy was not recommended in these cases.

There were three patients in this series (Cases 1, 2, and 4) who failed to show objective evidence of improvement, and yet obtained subjective relief after paravertebral block. Although lumbar sympathectomy failed to give relief in one of these cases (Case 2), a bilateral operation was performed in another case (Case 1) with excellent results. It is our feeling that subjective relief, as shown by an increase in "walking distance," affords a better index of the relief of symptoms to be expected from sympathectomy than does the claudication test. We have used this test, however, to obtain objective evidence of the significance of sympathetic vasoconstrictors in aggravating the symptom of intermittent claudication.

#### SUMMARY AND CONCLUSIONS

1. By means of a claudication test, objective evidence was obtained in seven cases that there was an increase in the ability of the muscles to work after procaine injection of the lumbar sympathetic ganglia. In three additional cases there was subjective improvement after the injection. Six of the patients who obtained relief from paravertebral procaine injection were subsequently subjected to lumbar sympathectomy, and on two of these a bilateral lumbar sympathectomy was performed. Immediate and persistent relief was obtained in five of the cases. There were no untoward results.

2. An explanation is adduced to harmonize the beneficial results of sympathectomy in our cases with the recognized physiologic effect of sympathetic stimulation, which produces an increase of blood flow through normal human muscle.

3. All except one of the patients who were studied showed evidence of obliteration of major arteries of the legs. In all but one of the cases there was clinical evidence of abnormal vasoconstriction, in addition to the organic vascular occlusion. Although it is true that intermittent

claudication is caused by arterial obstruction which is most frequently organic in character, in certain cases there may be an additional element of abnormal vasoconstriction which aggravates the circulatory deficiency. Lumbar sympathectomy gives promise of benefit in these cases.

#### CASE REPORTS

CASE 1.—H. T. (Graduate Hospital #122,459), a white man, aged 67 years, was admitted to the clinic with the chief complaint of intermittent claudication in both legs of two years' duration. His walking was limited to one block, and the pain was more severe on the left side. He gave a history of typical attacks of Raynaud's spasm of the digital vessels of both hands for thirty-five years. His feet were constantly cold and blue. He had developed a small lesion at the tip of the left second toe. Varicose veins of both sides had been treated by ligation and injection, without relief. He smoked from eight to ten cigarettes a day. Physical examination showed a frail, elderly man, with a marked atherosclerosis. Both femoral pulses were palpable, but no pulsation could be felt in the lower arteries of the legs. Oscillations were present at the right ankle but were barely perceptible on the left side. A vasodilatation test (heat applied to the arms) produced a rise of the skin temperature of the toes on the left side to 27.2° C., whereas, on the right side, the temperature came to only 21.9° after eighty minutes of heat. Roentgenograms of the lower portions of the legs showed calcification of some of the vessels. After paravertebral procaine block of the second, third, and fourth left sympathetic ganglia, the skin temperature rose to 28.5° C., but the claudication test showed no improvement, although the appearance of pain was delayed. He was surprised to find that his walking distance had been increased threefold for a period of one hour after the injection. One week later, 3 c.c. of a 2 per cent procaine solution were injected into the region of the left second, third, and fourth lumbar ganglia, and, when a good rise in skin temperature was obtained, 3 c.c. of 100 per cent alcohol were injected beneath the second and third ganglia. He was relieved of his claudication for three months. At the end of that time the claudication returned on the left side, and accordingly he was subjected to a left-sided lumbar sympathectomy. After recovery from this operation he was completely relieved of his claudication on the left side. Six months later, a right-sided lumbar sympathectomy was performed. At present, 1.5 years after operation, he can walk fifteen blocks without pain, and both feet are warm and of good color. The lesion of the tip of the left second toe has healed. Oscillations at the left ankle are still greatly reduced, but his symptoms have been relieved.

CASE 2.—H. McC. (Hospital of the University of Pennsylvania #45,188), a white man, aged 41 years, was admitted to the clinic with the chief complaint of claudication in the right hip and calf of three years' duration; this was increasing in severity, so that, when he was first seen, he was able to walk only 100 yards before he was stopped by pain. He did not complain of coldness of either foot. He had smoked one and one-half packages of cigarettes daily for fifteen years. Six months before admission he was found to have hypertension, with a systolic pressure over 200 mm. Hg. His father died of cerebral apoplexy at the age of 43. On physical examination there were marked sweating and cyanosis of both feet. On the right side the femoral pulse could be felt, but it was of poor quality. On the left side the dorsalis pedis pulsations could be felt. Roentgenograms showed no evidence of calcification of the vessels of the lower portions of the legs. His blood pressure was 180/110. The electrocardiogram was normal, and the orthodiagram

showed no enlargement of the heart. The eye grounds showed contracted vessels but no hemorrhages or exudate. The urine was normal and showed good concentration, and the phenolsulphonephthalein test showed 60 per cent excretion at the end of one hour and an additional 20 per cent at the end of two hours. The blood sugar was 98 mg. per cent. The blood Wassermann reaction was negative. After paravertebral procaine block of the eleventh and twelfth thoracic and first and second lumbar ganglia on the right side, the skin temperature of the toes rose to 32.5° C. Although the amplitude of contraction of the calf on stimulation was not materially increased, the pain which the patient developed during the first claudication test did not appear after the lumbar sympathetic block. His "walking distance" increased from 100 to 500 yards after the block. A right-sided lumbar sympathectomy was performed, and the first, second, and third lumbar ganglia were removed. Because of the hypertension the major and minor splanchnic nerves were resected at this operation. After operation, the blood pressure fell and became stabilized at 140/70, and his right foot became warm and dry. A pulsation in the medial and lateral geniculate arteries was felt. Sweating was absent on the right side below the groin. After operation his walking distance was still limited by muscular weakness, but the severe pain and numbness in the hip had disappeared.

CASE 3.—T. D. (Hospital of the University of Pennsylvania), a white man, aged 46 years, was admitted to the clinic with the chief complaint of claudication in the left hip and calf of one year's duration and claudication in the right calf of six years' duration.

The patient had noticed a gradual onset of intermittent claudication in the right calf six years previously, so that walking was limited to two blocks. At that time he was examined by Dr. Eugene M. Landis, to whom we are indebted for the following information. The right dorsalis pedis and posterior tibial pulses were not palpable. Those on the left were present. After procaine infiltration of the right posterior tibial nerve, the temperature of the toes increased to 32.3° C. The claudication test showed that there was some arterial occlusion in the right calf, but the left leg was normal. The patient gave a history of mild migraine, with two attacks of transient, left-sided hemiplegia, presumably as a result of cerebral vascular spasm. The diagnosis at this time was arterial occlusion, with marked vasospasm.

During the succeeding six years the claudication on the right side gradually disappeared, but one year prior to admission he developed severe claudication on the left side, involving the left hip and the left calf. His walking was then limited to one-half block. The left foot also became cold, white, and numb when it was exposed to cold. On examination, the dorsalis pedis pulse was present on the right, but the posterior tibial on the right and both ankle pulses on the left were absent, although an aberrant artery, just anterior to the left external malleolus, was palpable. Roentgenologic examination showed calcification of the dorsalis pedis arteries and the posterior tibial arteries in the lower third of the legs. However, there was no calcification of the vessels of the upper part of the leg, iliac vessels, or aorta. A vasodilatation test (heat applied to the arms) gave a normal response on the right side, but on the left side the skin temperature rose to only 28.2° C. The oscillations were better on the left side than on the right. The claudication test gave evidence of impairment on both sides, worse on the left than the right. After procaine injection of the left lower thoracic and upper lumbar sympathetic ganglia (twelfth thoracic and first, second, and third lumbar), there were lessening of the claudication and a marked increase in ability to walk. Instead of being stopped after half a block by pain in the left calf, he was now able to walk four blocks before the pain in the right calf brought him to a halt. The skin temperature after the procaine block rose to 33.1° C. A left-

sided lumbar sympathectomy was performed, and the first, second, and third lumbar ganglia were removed. His pain was relieved entirely on the left side, but he was still troubled by claudication in the right calf. Four weeks later a right-sided lumbar sympathectomy was performed, with removal of the first, second, and third lumbar ganglia. Since the second operation he has been able to walk as far as nine miles without intermittent claudication.

*Comment.*—This patient had been studied over a period of six years. Abnormal vasoconstriction was present when he was first seen, but the degree of arterial occlusion had varied. It was first more marked on the right, but thereafter had increased on the left side while collateral circulation had developed on the right side. There is a possibility that the arterial occlusion was precipitated by the abnormal vasoconstriction. That vasoconstriction exaggerated the disability was substantiated by the improvement which followed lumbar sympathectomy.

CASE 4.—J. L. (Hospital of the University of Pennsylvania #45,892), a white man, aged 65 years, was admitted to the clinic with the chief complaint of intermittent claudication in both legs of eight months' duration. Eight years earlier he had suffered a left-sided cerebral vascular accident, the exact nature of which was uncertain. On physical examination, no pulses were present on the left side below the femoral, but the posterior tibial pulse could be felt on the right side. Roentgenologic examination showed no evidence of calcification of the vessels of the lower portions of the legs. The blood sugar was 86 mg. per cent, and the Wassermann reaction was negative. Oscillometric examination at the ankles showed no oscillations on the left side and only  $\frac{1}{4}$  point on the right. The feet blanched on elevation, the left in fifteen seconds and the right in forty seconds; when they were brought back to the horizontal position there was delayed return of color, especially on the left side. The blood pressure was 102/70. Both feet were cold and moist, with an irregularly mottled appearance of the skin of the lower parts of the legs. The skin of the left toes was slightly edematous and shiny, and there was rubor on the left side. During a vasodilatation test the skin temperature rose to 29.2° C. on the right, whereas, on the left side, it rose to only 21° C. The patient received suction and pressure treatment of both legs for one month, without relief. A left paravertebral procaine block was performed by inserting three needles in the eleventh thoracic and first and second lumbar ganglia. The skin temperature of the left toes rose to 32.2° C. Although the claudication test showed no improvement, as a result of the injection he was able to walk three times as far without developing pain in the left calf.

*Comment.*—This patient, who showed marked evidence of organic vascular occlusion, also had an element of abnormal vasoconstriction. If he fails to improve with conservative treatment, lumbar sympathectomy will be advised.

CASE 5.—J. C. (Hospital of the University of Pennsylvania #41,114), a white man, aged 33 years, was admitted to the clinic with the chief complaint of intermittent claudication in the right calf after walking one block, and migratory phlebitis of three years' duration. In addition, the right foot was cold, blue, and painful. He had been treated with a 3 per cent saline solution and typhoid vaccine intravenously. A right-sided lumbar sympathectomy by the transperitoneal route had been attempted in another hospital, but the sympathetic ganglia had not been found because of dense adhesions. No relief from his vasoconstriction was obtained, although the lesion on the right foot subsequently healed. There were marked varicose veins of the right leg. Roentgenologic examination showed no evidence of calcification of the arteries of either leg. On the right side no pulses were palpable below the femoral, but on the left side both the dorsalis pedis and the posterior tibial pulses were present. There was marked blanching

of the right leg on elevation, with delayed return of color in the right foot, but the right foot was warmer than the left.

Oscillations on the right side were absent even above the knee, and there was only  $\frac{1}{4}$  unit on the left side at the ankle. There were increased sweating and cyanosis when he was exposed to the emotional stimulation of examination. A vasodilatation test showed that there was an adequate circulation on the left side, but a definitely impaired circulation on the right side; the skin temperature rose to only  $26.4^{\circ}$  C. on the right middle toe. Biopsy of a thrombosed vein of the leg substantiated the diagnosis of thromboangiitis obliterans. The claudication test showed slight impairment of the function of the left calf and marked impairment on the right side. After injection of the right twelfth thoracic and first, second, and third lumbar ganglia, the skin temperature rose to  $29.1^{\circ}$  C., and objective improvement occurred, as shown by the claudication test, although there was only a slight increase in his "walking distance."

The varicose veins of the right leg were eliminated by high ligation of the long saphenous vein. Some badly diseased tonsils were removed, and the patient was told to stop smoking entirely. Under this treatment his walking distance increased to two blocks, and the circulation in the right foot became fairly adequate.

*Comment.*—This patient improved on conservative treatment, which consisted of eradication of focal infection, cessation of smoking, proper care of the feet, and elimination of the varicose veins. It is our belief that sympathectomy would offer him only partial relief from his intermittent claudication, for the subjective relief after paravertebral block was only slight. Operation has been postponed for the present.

CASE 6.—F. D. (Hospital of the University of Pennsylvania #26,115), a white woman, aged 52 years, was admitted to the clinic with the chief complaint of cold feet and intermittent claudication, especially in the right calf, with pain after walking one-half block.

On examination, no pulses were palpable below the femoral on either side. She was given tissue extract injections and a long course of suction and pressure treatment without much relief. Her varicose veins disappeared after a high and mid-thigh ligation of the long saphenous veins. In spite of the elimination of her varicosities, the claudication was not lessened. A vasodilatation test showed impairment of the circulation on both sides; on the right side the temperature of the middle toe rose to only  $27.3^{\circ}$  C., and, on the left side, to  $25.4^{\circ}$  C. She received massive doses of vitamin B, intravenously, without improvement.

Paravertebral procaine block at the first, second, and third lumbar ganglia produced a good rise in the temperature of the toes. However, there was no increase in her walking distance. She still has intermittent claudication, after half a block, in the calves and feet on both sides.

*Comment.*—This patient presented evidence of widespread organic arterial occlusion, without clinical evidence of abnormal vasoconstriction. The fact that she was not relieved of her claudication by paravertebral procaine block, even though there was a good rise in the skin temperature of her toes, suggested that she would not be relieved by lumbar sympathectomy. Operation was not recommended.

CASE 7.—L. P. (Hospital of the University of Pennsylvania #44,330), a white woman, aged 40 years, was admitted to the clinic with a diagnosis of diabetes and a complaint of poor eyesight and numbness and tingling of the extremities. This patient's diabetes was discovered at the age of 13, and she had been under treatment with insulin and dietary regulation since 1922. About three years before admission she developed numbness and tingling in her extremities. Her feet were usually cold and became red on exposure to cold air or cold water. The numbness and tingling were not related to cold. On examination, vibratory sensation was

absent in both feet below the ankles and was decreased in the lower portions of the legs. Touch and pain sensations were also diminished. The reflexes were active. There was clinical evidence of abnormal vasocoustriction, with cold, moist, blue extremities. There was considerable intermittent claudication, so that she was stopped at the end of two blocks by pain in both calves. Both posterior tibial pulses were present, but the dorsalis pedis pulses could not be felt. Paravertebral procaine block on the right side produced a rise in skin temperature to 31.6° C., but no improvement was demonstrable by the claudication test. Her walking distance was not increased.

*Comment.*—In spite of the fact that this patient gave evidence of abnormal vasoconstriction, her chief complaint was not coldness of her feet, but numbness, tingling, and claudication. Because there was no response to paravertebral procaine block, lumbar sympathectomy was not advised.

CASE 8.—A. S. (Graduate Hospital #146,729), a white man, aged 37 years, was admitted to the clinic with the chief complaint of intermittent claudication in both calves of three years' duration, and a painful ulcer of the right great toe of one year's duration. He had received hot baths for this condition, without improvement. Examination showed extensive obliteration of the arteries. No pulses could be felt in either leg below the femorals. There was rubor of the right foot. A tender "crack" at the tip of the right great toe had shown no tendency to heal in six months. His walking was stopped after one block by intermittent claudication in the calves. He smoked a package of cigarettes daily.

The oscillometric reading at the right ankle was 3.5, and, at the left, only 1.5. A vasodilatation test (heat applied to the arms) showed that there was a good collateral circulation on the left, but only a fair one on the right. The claudication test showed marked impairment in the circulation to the left calf, but the blood vessels of the right side were less severely damaged. After paravertebral procaine block of the right twelfth thoracic and second and third lumbar ganglia, there was an increase in the temperature of the toes to 30.1° C., and the amplitude of contractions was slightly increased. However, he was now able to walk four blocks before he noticed pain in the right calf. He stopped smoking, but without relief of his pain. A right-sided lumbar sympathectomy was then performed. The first, second, and third lumbar ganglia were removed. After operation his walking distance was increased to eight blocks, and the lesion on the great toe healed.

*Comment.*—Even though the arterial occlusion was more marked in the proximal part of the left leg, the right foot was in more imminent danger because an open lesion due to vascular insufficiency was present. Sympathectomy was therefore performed first on this side. There was evidence of abnormal vasoconstriction on the left side, in addition to the arterial occlusion. If he does not improve, a left-sided lumbar sympathectomy will be advised.

CASE 9.—A. N. (Graduate Hospital #144,398), a white man, aged 32 years, was admitted to the clinic with the chief complaint of intermittent claudication in the right calf of one month's duration. The patient had had a sudden onset of pain in the right calf, with numbness and coldness of the right foot. His walking was restricted to a half block. Treatment by contrast bathing, tissue extract, and an arch support failed to give relief. On examination, the right femoral artery was found to be occluded above the popliteal. The left dorsalis pedis pulse was absent, although the left posterior tibial was normally palpable. The right ulnar pulse was absent. When he was first seen, he was smoking one and a half packages of cigarettes daily. Under instruction he stopped smoking, but his walking was still limited to one block. There was marked rubor of the right foot, with immediate blanching on elevation and delayed filling of the veins with dependency (thirty seconds). There was no evidence of acute migratory phlebitis, although

pigmentation as a result of previously inflamed veins was apparent on both legs. In addition, there was evidence of marked, abnormal vasoconstriction, as shown by cyanosis and increased sweating of both feet. Injection of procaine into the region of the right first, second, third, and fourth lumbar sympathetic ganglia brought about a prompt increase in the skin temperature to  $30.5^{\circ}$  C. A claudication test before the block showed marked limitations of muscle power. After paralysis of the sympathetic vasoconstrictor fibers, the amplitude of contraction was greatly increased, and he was able to walk three blocks without pain. The first and second right lumbar sympathetic ganglia were resected. He recovered from the operation without complications. His walking distance was immediately increased to eight blocks, and the right foot has remained warm and pink. He has been almost entirely relieved of his symptoms. Even though there is evidence of abnormal vasoconstriction on the left side, with loss of one of the ankle pulses, he has no symptoms in this leg, and, therefore, bilateral lumbar sympathectomy has not been recommended.

CASE 10.—L. T. (Hospital of the University of Pennsylvania #46,515), a white man, aged 42 years, was admitted to the clinic with the chief complaint of claudication in the left foot and calf of three years' duration. At first he could walk seven blocks, but recently had been limited to three blocks. The left foot was cold and numb. He had paresthesias over the left great toe. He smoked one package of cigarettes daily. Treatment had consisted of intravenous injections of citrate solution, from which he had obtained no relief. On examination, there was rubor on dependency, with blanching on the left in thirty seconds, and, on the right, in one minute. Rubor returned in eight seconds on the left side and in five seconds on the right. On the right side the posterior tibial pulse could be felt, but on the left side neither ankle pulse was palpable. The blood pressure was 122/96. Oscillometric readings at the right ankle were 4 units, and at the left, 0. A vasodilatation test (heat applied to the arms) showed that he was able to develop a normal blood flow on the right side; the temperature of the toes rose to  $32.5^{\circ}$  C. On the left side the temperature rose to  $27.6^{\circ}$  C. After injection into the left lumbar sympathetic ganglia, the skin temperature rose to  $30.8^{\circ}$  C., and the claudication test showed that a considerable increase in the amount of work could be performed. However, on walking, he was still stopped by the pain after three blocks. Although he presented evidence of abnormal vasoconstriction, it was felt that sympathectomy would not relieve him of his intermittent claudication, and, therefore, it was not advised.

CASE 11.—C. K. (Hospital of the University of Pennsylvania), a white man, aged 59 years, was admitted to the clinic with the chief complaint of intermittent claudication in the left calf, foot, and thigh of five years' duration. The patient noticed a gradually increasing weakness and discomfort in the left calf on walking uphill. There was no history of migratory phlebitis, nor did he complain of coldness in either foot. On examination, he was found to have a blood pressure of 150/80. The pulses were normal in the upper extremities. The right dorsalis pedis pulse was not palpable, and no pulsation could be felt on the left side below the femoral. There was abnormal blanching of the left foot on elevation, but filling on both sides returned within eighteen seconds. The oscillometric readings at the ankles on both sides were approximately normal. The claudication test showed abnormal fatigue, with pain, on the left side, and some fatigue, without pain, on the right side. The vasodilatation test (heat applied to the arms) showed a normal response on the right side, but on the left side there was no increase of the temperature of the toes. Roentgenograms showed no calcification of the vessels. Injection of procaine into the region of the left eleventh and twelfth thoracic and first and second lumbar sympathetic ganglia resulted in a good rise of skin



temperature, with disappearance of sweating and dilatation of the veins of the lower leg. Considerable improvement was demonstrated by the claudication test, and his walking distance was definitely increased, so that, instead of being stopped by pain after climbing two flights of stairs, he was able to climb four flights without discomfort. Lumbar sympathectomy was advised, but the patient decided to try conservative treatment.

CASE 12.—A. M. (Hospital of the University of Pennsylvania #41-48,766), a white man, aged 60 years, was admitted to the clinic with the chief complaint of intermittent claudication in both calves and the right thigh of three months' duration. The onset of symptoms had been gradual, and, when he was seen, his walking was limited to two blocks. He had received no treatment for this condition. He smoked approximately ten pipefuls of tobacco per day. On examination, all ankle pulses were present, but the feet were cold and blue, although they were not moist. The veins were markedly contracted (Fig. 1). The oscillations at the ankles were normal on the left side and only slightly reduced on the right side. The blood pressure was 128/70. Roentgenograms of the legs showed no calcification of the vessels of the lower portion of the leg and foot.

The blood urea nitrogen was 11 mg. per cent, and the phenolsulphonephthalein excretion, 77 per cent. The heart was moderately enlarged (+21 per cent in the orthodiagram), and there were slurring of the QRS complex in the electrocardiogram and benign sclerosis of the retinal vessels.

After the injection of procaine into the region of the right first, second, and third lumbar ganglia, the skin temperature of the toes rose to 32.2° C., and the oscillation at the ankle increased from 3 to 9 units. His walking distance was increased from two to eight blocks immediately after the injection, and the claudication test showed a considerable increase in the amplitude of contraction. The first, second, and third lumbar ganglia on the right were resected, and, after the operation, he was completely relieved of his intermittent claudication on this side.

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#### DISCUSSION

DR. KENNETH W. THOMPSON, New Haven, Conn.—There is one other aspect of this problem to which, I believe, we should pay attention, namely, the possible hormonal relationship between muscle metabolism and blood flow. I have in mind a patient, a eunuchoid, who began treatment with testosterone at the age of about 29, after which there was no question in anyone's mind that his leg muscles hypertrophied. You may also recall the fact that in the female guinea pig the masseter muscles hypertrophy while the animals are being treated with testosterone. We are also familiar with the atrophied muscles of elderly men.

There seems to be no question now that the giving of testosterone changes the nitrogen balance of the body, causes a storage of nitrogen, and greatly alters muscle metabolism. Dr. Albright, of Boston, has given us some astounding data on this subject. It may be that this sort of hormonal relationship has something to do with whether or not sympathectomy produces the desired results. Suppose an elderly man who had been deficient in one of those postulated hormones for ten or fifteen years develops complaints referable to muscle pain, and sympathectomy is done. It probably does not alter his muscle metabolism very much. When the patient is younger, with a complaint caused by occlusion, perhaps from Buerger's disease or trauma, sympathectomy may very well result in a great deal more benefit, purely from the effect of the sympathectomy on blood flow.

This hormonal balance may have a bearing on some of the other phases of the problem, such as the collateral circulation of the heart. I believe we must not neglect this phase of the subject in discussing sympathectomy.

DR. NORMAN E. FREEMAN, Philadelphia.—The question whether parasympathetic nerves supply blood vessels of muscles and produce vasodilatation has not been answered. Years ago I was interested in this problem from the standpoint of

blood pressure reactions in sympathectomized animals and did find evidence that there was some system outside the sympathetic nervous system which could cause changes in blood pressure. I am not sure what part such nerves might play in the production of vasodilatation in muscles after removal of the sympathetic fibers.

The clinical observation that anterior root section will produce much the same circulatory pattern in the lower extremities as that obtained from sympathectomy, however, would suggest at least that efferent fibers traverse the anterior roots.

As far as Dr. Thompson's comments are concerned, I believe his observations on the effect of testosterone on intermittent claudication are very interesting. The patients on whom we have operated were not only patients with Buerger's disease, but patients with arteriosclerosis, as well. Lumbar sympathectomy, although it apparently will cause sterility, does not necessarily affect potency. One of the patients who was operated upon was 71 years old. He had no pulse in his left leg, but he had evidence of severe arterial vasoconstriction. He gave a history of Raynaud's disease in his hands for thirty-five years, and the feet were typically cold, blue, and moist, with contracted veins. The response in his case makes one feel at least that there is some vasoconstrictor activity which is interfering with the normal supply of blood to the working muscles.

## CEDILANID, WITH SPECIAL REFERENCE TO ITS INTRAVENOUS USE

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THE use of the ordinary whole leaf of digitalis, the digitalis purpurea of the United States Pharmacopeia, has never been considered ideal for several reasons. First, it required bio-assay; second, it was impure and hence could not be given intravenously with assurance; third, its potency has varied from time to time, as shown by the fact that the U.S.P. XI digitalis is one-third stronger than that of the U.S.P. X. In recent years the glycosides of digitalis have been isolated in pure crystalline form, and work is being done with these pure substances. In addition to the ordinary digitalis, digitalis purpurea, there is another plant, digitalis lanata, which is indigenous to the Balkan countries. Stoll<sup>1</sup> has isolated the glycosides of this new digitalis. There are three glycosides in each, but digitalis lanata differs in that it alone contains lanatoside C, or cedilanid. Clinical interest in lanatoside C began with the pharmacologic work of Moe and Visscher<sup>2</sup> on heart-lung preparations. This suggested that lanatoside C was the least toxic and the most potent of the lanata glycosides and could be obtained in pure crystalline form.

Early preliminary work in Europe<sup>3</sup> (the drug was first available in Switzerland) indicated that lanatoside C was a potent drug. It has been used in the United States for the past two years. Gold and his co-workers,<sup>4</sup> in New York, and Fahr and LaDue,<sup>5</sup> in Minneapolis, have made preliminary reports. During the past two years we have been studying the oral and intravenous use of lanatoside C at the University of California Hospital, and our reports are based on that work.<sup>6</sup> To date we have followed eighty-five patients. The drug\* comes in tablets of 0.5 mg., as well as in 2 c.c. and 4 c.c. ampoules which contain 0.2 mg. per cubic centimeter. It has been established that the cat unit is equal to 0.28 mg.; however, Gold showed that 1 mg. of cedilanid is equal to 293 mg. of digitalis leaf when they are compared by the cat method, to 438 mg. when they are compared by the frog method, and to 170 mg. when they are compared in man by oral administration. Therefore, the clinical potency of these pure glycosides should be ascertained by clinical assay and not by animal assay.

The intravenous administration of cedilanid has proved to be of great value. We have used it in thirty-eight cases in doses up to 14 c.c. per

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\*Marketed by the Sandoz Chemical Works, Incorporated, to whom we are grateful for supplies.

day, some of which were divided. In general, 8 e.e. per day is the digitalizing dose, and 6 e.e. to 14 e.e. in twenty-four hours in divided doses will digitalize almost all patients. In only three instances was mild nausea produced by 8 e.e. of cedilanid given in one dose, and in many instances beneficial effects were noted in ten to twenty minutes. In auricular fibrillation the ventricular rate may fall 40 to 50 beats within thirty minutes to two hours; in auricular flutter a fixed 4 to 1 block, and, subsequently, normal rhythm may be produced by a single dose of 8 e.e. administered intravenously. In cases of normal rhythm with congestive failure, digitalization may be accomplished within twenty-four hours. The advantages of rapid, safe digitalization are self evident in cases of desperate cardiac failure. Frequently, partial digitalization may be accomplished by the intravenous administration of 4 e.e. to 6 e.e., and then maintained by the oral preparation. The intravenous preparation is not recommended for maintenance because frequent injections are necessitated by the rapid excretion of the drug. It is, therefore, better to use the oral preparation of cedilanid for maintenance. In general, we find that a daily maintenance dose of 1 e.e. to 3 e.e. is needed when the drug is given intravenously.

#### CONCLUSIONS

1. Cedilanid is a pure, crystalline glycoside which is obtained from *digitalis lanata* and is not present in *digitalis purpurea*.
2. Cedilanid is marketed in tablets of 0.5 mg. for oral use, and in ampoules in which each cubic centimeter is equal to 0.2 mg.
3. The intravenous digitalizing dose varies from 8 e.e. to 14 e.e. in twenty-four hours.
4. Rapidity of action is the most striking clinical feature of cedilanid.

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# CLINICAL EXPERIENCE WITH THE ORAL ADMINISTRATION OF CEDILANID, AND A COMPARISON OF THE ORAL AND INTRAVENOUS PREPARATIONS OF CEDILANID WITH DIGITALIS PURPUREA

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**I**N OUR first paper<sup>1</sup> the history and pharmacology of cedilanid and the use of the intravenous preparation were discussed. In this paper we shall summarize our experience with the oral administration of cedilanid and compare the oral and intravenous preparations with digitalis purpurea.

The digitalizing dose was ascertained in forty-five cases. Nine patients were digitalized in twenty-four hours with a dose varying from 4 to 7 mg.; six patients, in forty-eight hours with 5 to 15 mg.; fifteen patients, in seventy-two hours with 5.3 to 9.3 mg.; five patients, in ninety-six hours with 6 to 16 mg.; and three patients, in 120 hours with 9 to 10 mg. The maintenance dose was ascertained in forty-seven cases. It varied from 0.5 to 2.5 mg.; the average was 1.6 mg. (3 tablets) daily. Assuming an average maintenance dose of 1.6 mg., and calculating all doses for a period of seventy-two hours, we obtained an average digitalizing dose of 7.5 mg.

Therefore, we conclude that a satisfactory method for the administration of cedilanid would be to give 6 to 7.5 mg. in about seventy-two hours. If the tablets of 0.5 mg. which are now on the market are used, a total of 12 to 15 tablets would be required. Eight tablets, or 4.0 mg., may be given on the first day in divided doses, and 4 tablets daily thereafter. When therapeutic effects are evident, or if initial toxic manifestations appear, the dosage should be decreased.

Since the acceptance of Withering's work, many substitutes, with elaborate claims of advantage over digitalis purpurea, have appeared on the market, but none has proved superior and nearly all are much more expensive. An exact comparison between the action of cedilanid and that of digitalis purpurea on human beings is difficult because patients do not have consecutive, identical attacks of congestive failure. In twenty-one cases in which the manifestations were reasonably parallel, the average maintenance dose of cedilanid was 1.6 mg., and, of digitalis

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<sup>2</sup>Presented before the meeting of the California Heart Association, Del Monte, Calif., May 4, 1941.

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purpurea, 0.13 Gm. This is 5.7 eat units of cedilanid to 1.3 eat units of digitalis purpurea. The toxic manifestations were similar. Of ninety-five patients who were treated with cedilanid, approximately one-third showed toxicity. This percentage was necessarily high because of experimentation with the dosage. The toxic manifestations disappeared in one to three days, which was about the same period of time as when patients were treated with digitalis purpurea. Prolonged A-V conduction developed in five cases; A-V nodal tachycardia, in one; and auricular fibrillation, in one. The arrhythmias in the last two cases reverted to normal spontaneously in forty-eight to seventy-two hours. The electrocardiographic changes were similar; the T waves, S-T segments, and P-R intervals were affected.

The therapeutic effects of cedilanid and digitalis purpurea were similar, with one important exception. The intravenous preparation of cedilanid acts more rapidly, as was pointed out in our previous paper.<sup>1</sup> Standardization of cedilanid by the gravimetric method appears to be advantageous because it insures constant potency, the lack of which is a recognized disadvantage of digitalis purpurea.<sup>2</sup>

#### CONCLUSIONS

1. Cedilanid is effective orally in all conditions which are commonly treated with digitalis purpurea.
2. The oral digitalizing dose averages 7.5 mg. in seventy-two hours.
3. The average oral maintenance dose is 1.6 mg.
4. The rapid absorption, constant potency, and rapid action of cedilanid give it advantages over digitalis purpurea.

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# ACUTE PERICARDITIS SIMULATING ACUTE CORONARY OCCLUSION

## A REPORT OF FOURTEEN CASES

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WITHIN recent years we have come to the conclusion that there is, in adults, a distinctive form of acute pericarditis of benign, non-suppurative nature. In a considerable percentage of these patients, pain in the chest is the most outstanding complaint. Thus, there are occasional patients with precordial pain regarding whom the crucial question arises whether the diagnosis should be acute coronary occlusion or acute pericarditis. The problem is complicated still further by the well-known fact that patients who have acute coronary occlusion may have pericarditis as a complication. The importance of making the correct diagnosis is obvious.

We are reporting fourteen cases in which the differential diagnosis of acute coronary occlusion and acute pericarditis was of paramount importance. In nine of these cases we feel that it can be stated unequivocally that the condition was acute pericarditis; in two cases, that coronary occlusion could be ruled out and that the evidence for acute pericarditis seemed acceptable; and in three cases that acute pericarditis had occurred, but that an associated coronary occlusion had not been excluded definitely, although, in our clinical judgment, it was unlikely. In most of these cases the attending physician was justly in a quandary as to the correct diagnosis. In a few cases in which the attending physician heard a pericardial friction rub, he considered that the proper diagnosis was pericarditis, until doubt was raised in his mind by the electrocardiographic changes which developed. We believe that the type of illness associated with acute pericarditis in adults, accompanied by pain, is crystallized sufficiently in its clinical and electrocardiographic manifestations to justify a detailed report of the cases.

### REPORT OF CASES

The study included nine cases of pain in the chest simulating coronary disease, in which the diagnosis of acute pericarditis is considered as established.

CASE 1.—The patient was a man, aged 44 years, with no history of previous illnesses. He caught a head cold and possibly had a slight fever on June 3, 1939.

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A week later he developed an intermittent, dull, substernal pain which lasted fifteen to twenty minutes at a time and was not aggravated by effort or relieved by acetylsalicylic acid and codeine. Examination by his physician was negative. By June 24, a progressive, general malaise had developed, and the patient's temperature was found to be 101° F. The following day he was admitted to the hospital, where a pericardial friction rub was found; his temperature was 102.2° F., and his pulse rate, 120. He was given 90 grains (6 Gm.) of sulfanilamide in a period of twenty-eight hours, after which his temperature became normal and remained so. After being in the hospital three weeks, he was dismissed feeling well. He returned to a full, active life without dyspnea or effort distress of any kind and has remained well.

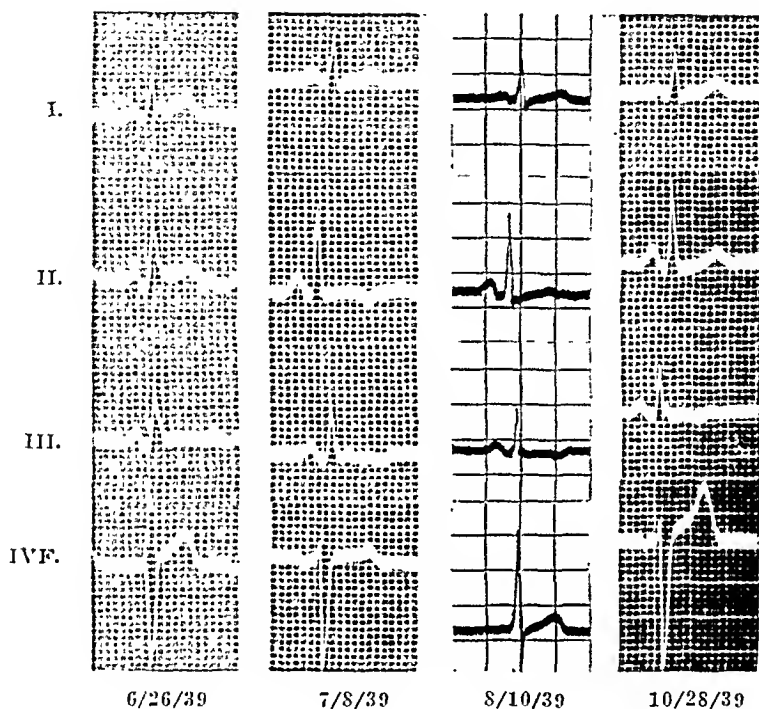


Fig. 1.—Sequence of electrocardiographic changes in Case 1.

The electrocardiograms taken during the patient's illness and after his recovery are reproduced in Fig. 1. The elevation of the S-T segment, particularly in Leads I and II, with the convexity downward, followed, in subsequent electrocardiograms, by negativity of  $T_1$  and  $T_2$ , and, finally, by a return to normal, is characteristic of pericarditis and does not fit into any observed sequence of tracings in coronary occlusion.

CASE 2.—A physician, aged 35 years, gave the history that nine years previously, three weeks after tonsillectomy, he had been in bed for one week because of a low substernal pain which never had been explained. It was said that he had no fever and that the roentgenogram of his chest and the electrocardiogram were normal.

The patient's present illness began Dec. 28, 1939, with a common cold which kept him away from his office for two days. A week later (Jan. 3, 1940) he was admitted to the hospital because of a mild pain in his chest of eighteen hours' duration. With the onset of the pain there was a recurrence of soreness of his throat. On admission the patient's temperature, the roentgenogram of his chest, and the electrocardiogram were normal, and the leucocytes numbered 18,000 in each cubic millimeter of blood. On the following day his temperature reached

99.4° F., and the pain in his chest was accentuated by turning to either side in bed, or by swallowing, particularly with the head extended. On the third day in the hospital (January 5) morphine was required for relief of the pain, and a pericardial friction rub was heard for the first time. The low-grade fever and friction rub persisted for five days. The pain gradually disappeared within three weeks. The patient returned to work April 15, 1940, feeling well. One year later (April, 1941) he informed us that he had no further symptoms of any kind.

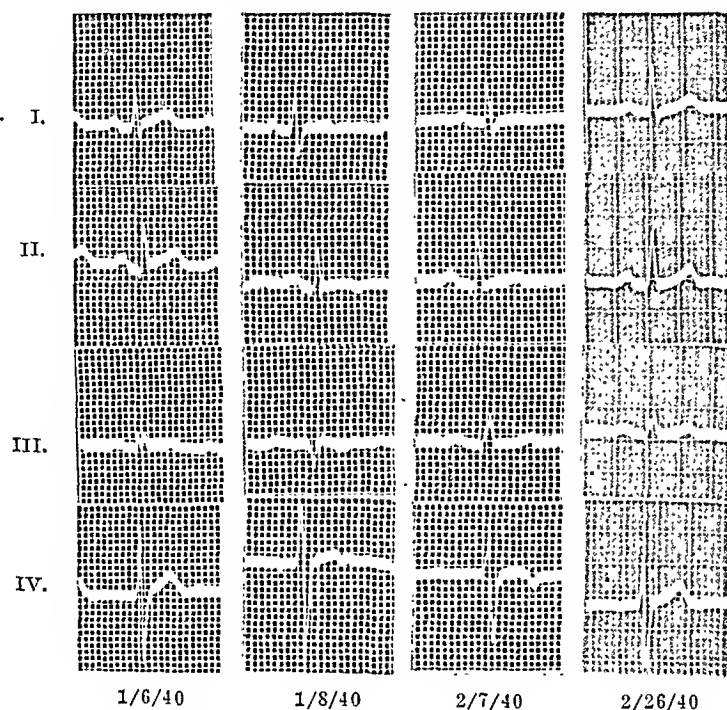


Fig. 2.—Sequence of electrocardiographic changes in Case 2.

The series of electrocardiograms (Fig. 2) shows what we consider a typical picture of pericarditis in all of its stages. The early elevation of the S-T segment in all of the standard leads, and some decrease in the amplitude of the QRS complexes, followed, in subsequent tracings, by inversion of the T wave in all leads, including the chest lead, with return to normal, are practically diagnostic. At no time did a Q or T pattern of coronary occlusion develop.

CASE 3.—The patient was a man, aged 26 years. In the first week of June, 1940, a sore throat and infection of the upper part of the respiratory tract, associated with considerable malaise, developed. On June 21 the patient complained of dull pain under the upper end of the sternum and a sense of retrosternal oppression. On the following day he had an attack of sudden dyspnea of very short duration and was admitted to the hospital. At this time there were slight fever, moderate leucocytosis, and considerable elevation of the sedimentation rate. The only physical sign of note was an accentuated, diastolic, third heart sound. The temperature and leucocyte count were normal twenty-four hours later.

On June 27 the patient was dismissed from the hospital without symptoms, and he returned to work in October. Throughout November and December he continued to work but complained of an occasional precordial burning sensation and of localized precordial pain. However, by April, 1941, he was considered in normal health. The electrocardiograms (Fig. 3) showed changes which, on rapid analysis,

readily could be believed to indicate coronary occlusion, because elevation of the S-T segment in Lead I was accompanied by reciprocal S-T depression in Lead III in the first tracing. Against such a deduction are the absence of a Q pattern in any of the electrocardiograms, the absence of changes in the precordial lead indicating coronary occlusion, the development of negativity of the T wave in all standard leads, and, finally, the relative normality of the tracing at the end of three months.

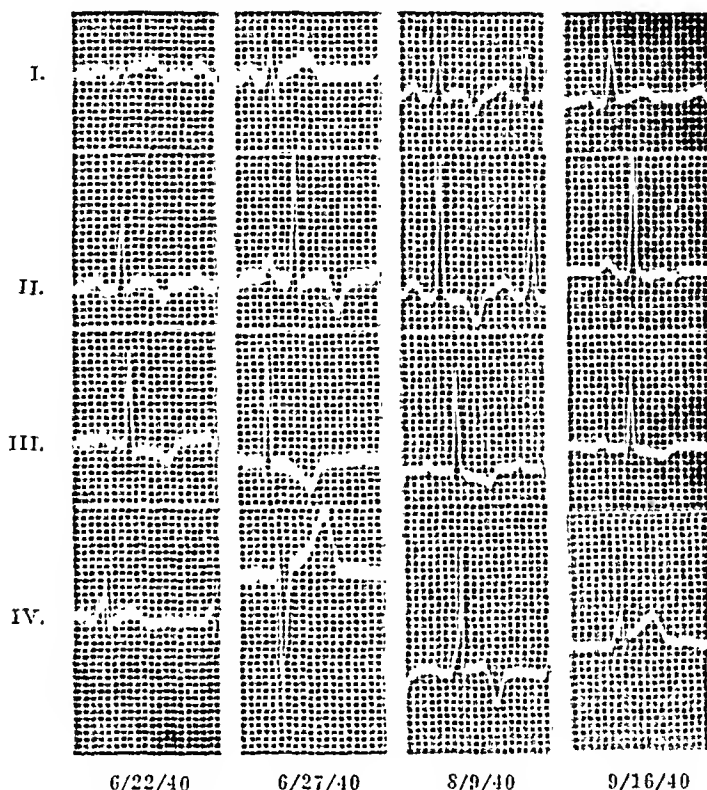


Fig. 3.—Sequence of electrocardiographic changes in Case 3.

CASE 4.—The patient was a farmer's wife, aged 47 years, who previously had been well except for some fatigue of a few months' duration. On Aug. 5, 1940, chilly sensations developed, followed by retrosternal pain extending to the back and slightly to the neck. This pain was aggravated by deep breathing and kept her awake that night. On the following morning she visited a physician who afforded her immediate relief by applying mustard plasters. Early in the morning of August 8, intermittent tachycardia developed, and the patient had a slight nonproductive cough and perspired freely. She registered at the Mayo Clinic on this day. On examination, a loud pericardial friction rub was heard, and her temperature was 101° F. A low-grade fever, friction rub, and intermittent attacks of auricular fibrillation persisted for ten days. The sedimentation rate was elevated to as high as 66 mm. in one hour, but there was no leucocytosis. The patient was comfortable and without complaints within a few days and had no pain after the first day. After three weeks in the hospital she was dismissed feeling well, and her general physical examination gave negative results. In April, 1941, she was feeling well and was active in her work. At this time also, physical examination was negative.

The series of electrocardiographic tracings (Fig. 4) shows a sequence of changes which are characteristic of acute pericarditis. There was, in the early stages, a

slight elevation of the S-T segment, with a concave upper edge, in Leads I and II, followed by the development of negativity of the T wave in all leads. In the second tracings auricular fibrillation was present. In the last tracing the electrocardiogram had returned to normal.

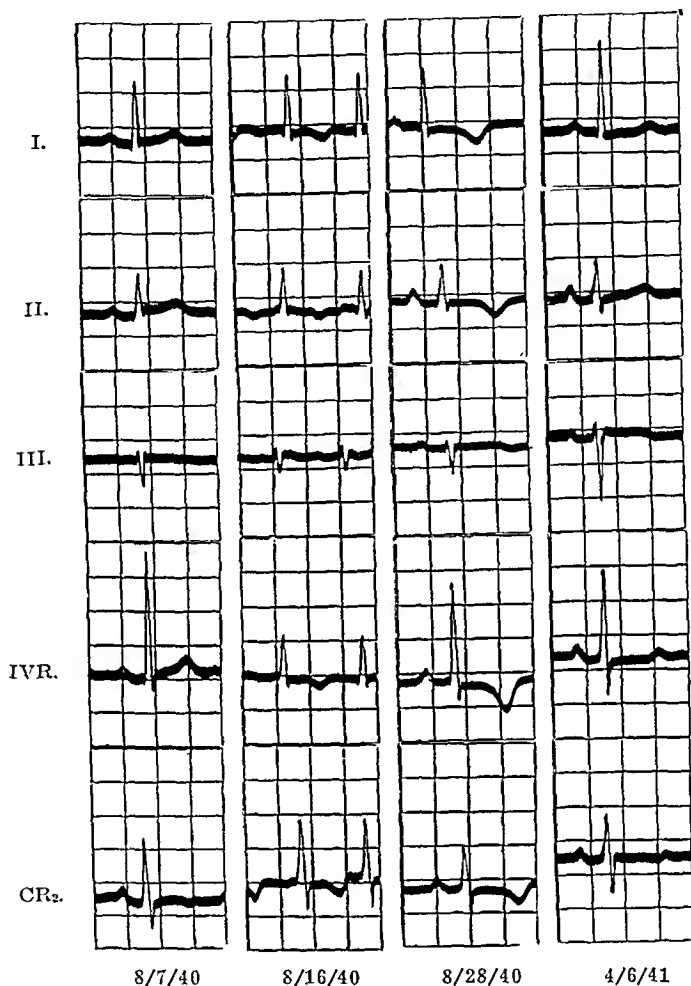


Fig. 4.—Sequence of electrocardiographic changes in Case 4.

CASE 5.—The patient was a physician, aged 38 years. In February, 1939, he had a "cold" and sore throat which were severe enough to confine him to his home for a few days, and for which some sulfanilamide was taken. About two weeks later he began to have general malaise and fatigue, followed, two or three days later, by pain in the chest which began gradually and was localized in a small region beneath the left nipple. The pain was moderately sharp, made the patient uncomfortable, and was aggravated by change in posture or by almost any body movement. There was no accentuation as a result of swallowing or deep breathing.

The pain persisted with varying severity for about four weeks, during which time the patient was confined to his home. There was no fever, and the leucocyte count and sedimentation rate were normal. He gradually improved to the point of general well-being, but there were occasional mild recurrences of the pain for the next four or five months. Roentgenoscopic and roentgenkymographic examinations and roentgenograms of the chest and heart gave negative results, except that a small pericardial plaque was noticed in September, 1940. From August, 1940,

to February, 1941, the patient felt exceptionally well and was free from pain. In March, a mild head cold developed, and a week later there was a recurrence of painful precordial distress lasting several hours. After this short attack the patient again became symptomless and was feeling well when last heard from (April, 1941).

In the early part of the patient's illness the diagnosis was left in abeyance; the possibility of occlusion of a small coronary vessel was suspected. The more complete development of the clinical picture, together with the evolution of the electrocardiographic pattern, seemed to indicate acute pericarditis, and, in retrospect, it is believed that the whole picture supports this diagnosis.

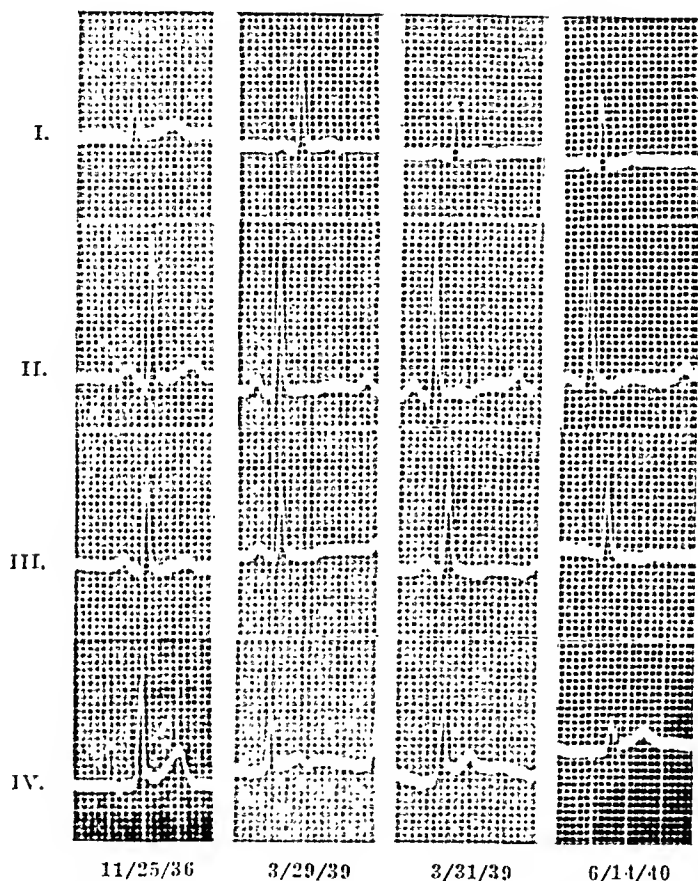


Fig. 5.—Sequence of electrocardiographic changes in Case 5.

The electrocardiograms (Fig. 5) showed early elevation of the S-T segment in Leads I and II and in the chest lead, and, later, negativity of the T wave in all the limb leads. The chest lead in this instance showed persistent elevation of the S-T segment. There was no Q or T pattern of coronary occlusion.

**CASE 6.**—A civil service worker, a man, aged 46 years, had sustained a fracture of the left tibia, followed by osteomyelitis, twenty-three years previously. The fracture had healed satisfactorily at that time. In September, 1940, an infection of the soft tissue of the left leg developed but responded to treatment by wet dressings and drainage. On Dec. 2, 1940, there was recurrence of cellulitis of the left leg, with fever, and the patient was referred to the hospital.

On this same evening there was a gradual onset of severe substernal pain, with extension to the interscapular region and throat. There was some cyanosis; the

patient's temperature was 102° F.; and he appeared ill. The condition was believed by the house physicians to be coronary occlusion. This diagnosis seemed to be supported by a convulsive attack with syncope, in the middle of the night. When the patient was seen by one of us, a definite pericardial rub was heard, and, because of the patient's fever, it was believed that the whole picture was compatible with acute pericarditis. This opinion was supported by electrocardiographic evidence, and, we believe, was fully substantiated later by the patient's clinical

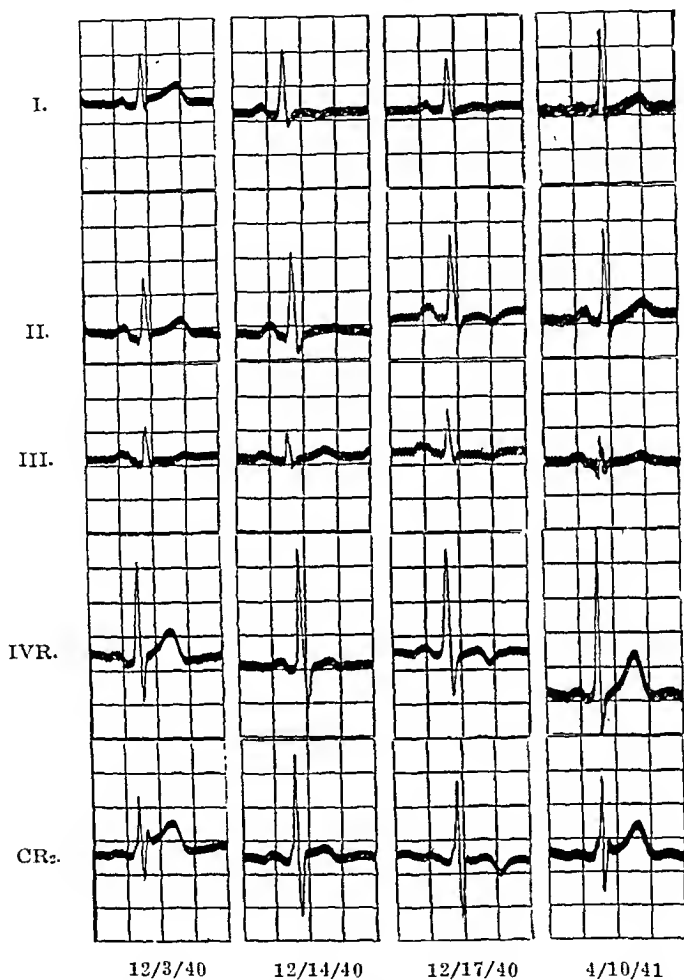


Fig. 6.—Sequence of electrocardiographic changes in Case 6.

course. He was under observation in the hospital for thirty days. During this period he had recurring attacks of precordial pain, periods of low-grade fever, and, at times, pain in the left shoulder tip at the onset of inspiration. During this time there was no leucocytosis, but the sedimentation rate was elevated persistently, averaging 63 mm. in one hour. The patient was given 60 to 75 grains (4 to 5 Gm.) of sulfathiazole daily for six days, with a questionable effect on the fever, and no evidence of general clinical improvement. During this time there was a slight, globe-shaped enlargement of the heart. On one occasion, when there was a recrudescence of the fever, we considered the advisability of doing a pericardial tap, fearing the onset of suppuration, but this was deferred and improvement spontaneously occurred.

During January, 1941, the patient continued to have ill-defined attacks of precordial pain but otherwise felt fairly well. He was allowed to return to work

in February and has continued to feel well except for occasional aching precordial distress.

The electrocardiograms (Fig. 6) showed the characteristic early elevation of the S-T segments, the late negativity of the T wave in all limb leads, and return of the electrocardiogram to normal.

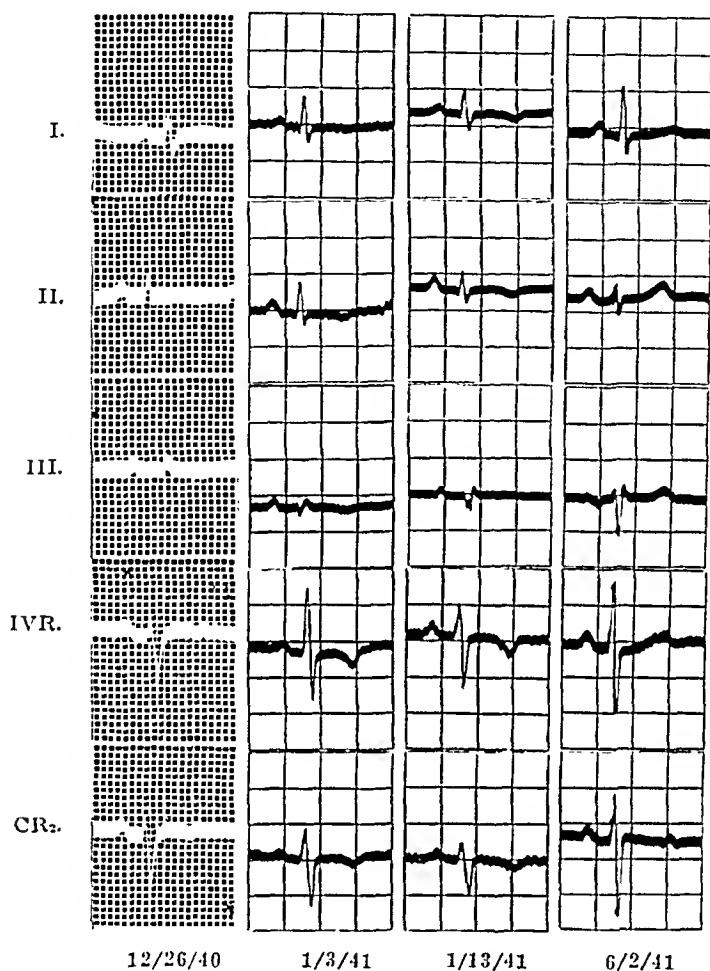


Fig. 7.—Sequence of electrocardiographic changes in Case 7.

CASE 7.—A man, aged 40 years, was admitted to the hospital Dec. 24, 1940, with the history that for the preceding ten days he had been in bed, feeling weak and having chills and fever. On the day of admission there had developed a dull, rather constant substernal pain which was not affected by respiration but was partly relieved when the patient lay on the right side. He appeared pale and ill; the pulse rate was rapid; and there was a loud pericardial friction sound. There had been no dyspnea previous to his coming to the hospital. The home physician had suspected coronary occlusion. The cardiac silhouette was considerably enlarged. The patient was observed in the hospital for four weeks, during the first week of which time there were low-grade fever, moderate tachycardia, and an increased sedimentation rate (30 mm. in one hour). No leucocytosis occurred. He was dismissed feeling well, and his cardiac silhouette was of normal size at that time. When seen last, in June, 1941, he appeared to be in excellent health, was working full time, and made no complaints. Examination of the heart gave negative results.

The series of electrocardiographic tracings (Fig. 7) showed gradual development of negativity of the T wave in all derivations, and, later, return of the tracing to

normal. The first tracings showed low amplitude of the QRS complexes in all three leads and isoelectric T waves but no elevation of the S-T segment. Whether the latter had occurred earlier in the disease would be impossible to say.

CASE 8.—A physician, aged 45 years, had a long history of previous illnesses, including repeated attacks of tonsillitis. In 1909 he was thought to have had pulmonary embolism after appendectomy. In 1921 he had scarlet fever, followed by rheumatism. In 1927, eleven days after the repair of a right inguinal hernia, sudden substernal pain developed, and it was believed that he had had pulmonary embolism. At this time a systolic click was heard, which later gave place to a pericardial friction rub. Low-grade fever persisted for twelve days. Definite saphenous thrombophlebitis occurred on the nineteenth postoperative day. Several electrocardiograms, taken at intervals of a month or more, did not reveal anything of diagnostic value.

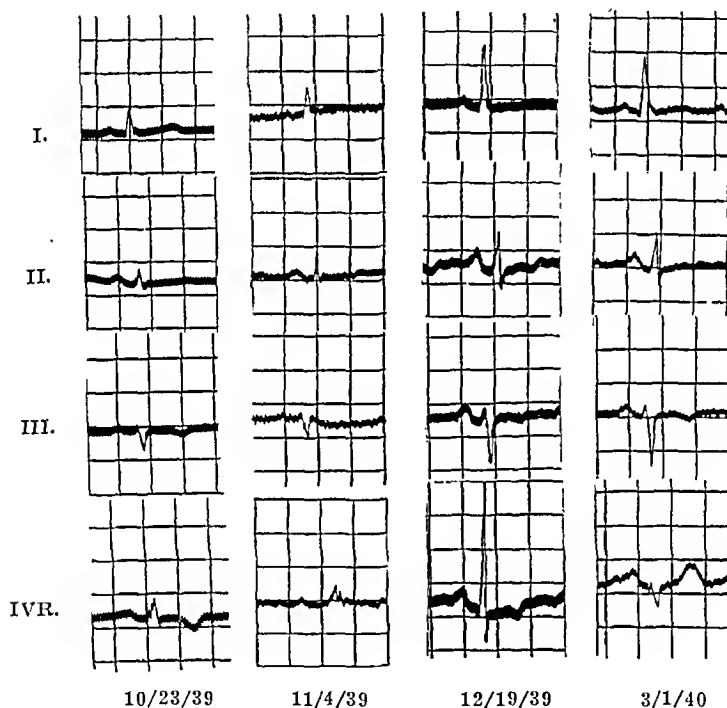


Fig. 8.—Sequence of electrocardiographic changes in Case 8.

The illness, during which we have complete electrocardiographic studies, began Oct. 1, 1939, as influenza and sinusitis; it confined the patient to bed and was associated with a temperature of 101° F. Between October 22 and November 6, he had several short attacks of auricular fibrillation and tachycardia and developed a dull retrosternal discomfort, which was increased by effort. In January, 1940, the patient was still experiencing the retrosternal pain on exertion, and it persisted for three to six hours after resting. In March he had a recrudescence of general malaise and low-grade fever and was in bed for ten days. After this, gradual improvement occurred, but there was still considerable general asthenia which responded slowly to a regimen of rest.

The electrocardiograms (Fig. 8) differed from those in the other cases in that they did not show any of the changes generally associated with acute pericarditis, but rather those of chronic pericarditis, namely, low amplitude and isoelectric or inverted T waves in all leads. The return toward normal in this series of tracings was particularly striking.



CASE 9.—A farmer, aged 52 years, registered at the clinic Jan. 14, 1930. He gave the history that on Oct. 7, 1929, he had suffered from dull pain in the epigastrium, associated with general malaise and low-grade fever. There was, at times, pain at the tip of the left shoulder, between the shoulder blades, and on both sides of the chest. There were orthopnea, weakness, sweats, and a heavy sensation in the chest. The pain and low-grade fever persisted intermittently for the next three months. Examination in the clinic in January gave negative results except for distant heart sounds. The leucocyte count, the results of roentgenoscopic examination, and the roentgenogram of the chest were normal.

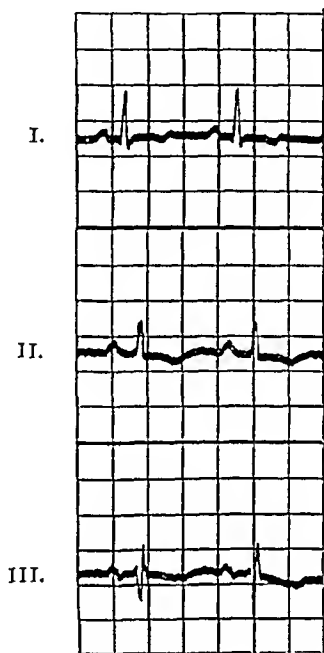


Fig. 9.—Electrocardiographic changes in Case 9.

The patient gradually improved in the hospital, although the diagnosis remained uncertain. Inasmuch as his pain had been accentuated by exercise, a true effort angina was suspected, and finally, because of his electrocardiographic abnormalities, a diagnosis of coronary occlusion was made.

In 1935 we obtained the information from the patient's home physician that since his visit to the clinic he had been exceptionally well and was working every day without any trouble. In July, 1941, he was still in good health, without any symptoms of heart disease, and, in retrospect, we believe that he had an attack of acute pericarditis in 1930.

The electrocardiogram (Fig. 9), taken in 1930, showed negativity of the T waves in the three limb leads, and we should consider the picture compatible with acute pericarditis in its later stages.

Two cases of pain in the chest simulated coronary occlusion, but this diagnosis is regarded as untenable; the series of electrocardiographic tracings indicated that the patients had pericarditis.

CASE 10.—A man, aged 25 years, while en route to work on April 22, 1940, became aware of substernal discomfort which rapidly progressed in severity. He was seen by his physician 1.5 hours after the pain began, at which time the results of physical examination and the blood pressure were normal. The pain was located in an area about the size of the hand, lying transversely over the xiphoid process.

It was described as a sensation of compression in the chest, was not projected, and was aggravated by the supine position and by inspiration. The discomfort was severe for about six hours but had disappeared completely within about eighteen hours. No friction rub was ever present during subsequent examinations, and fever, leucocytosis, and an increase in sedimentation rate did not occur. Three roentgenologic examinations of the chest in a short period after the attack gave negative results, and no abnormality in the cardiac silhouette was present. The patient recovered quickly, and, when last heard of through his home physician in April, 1941, he had remained completely well.

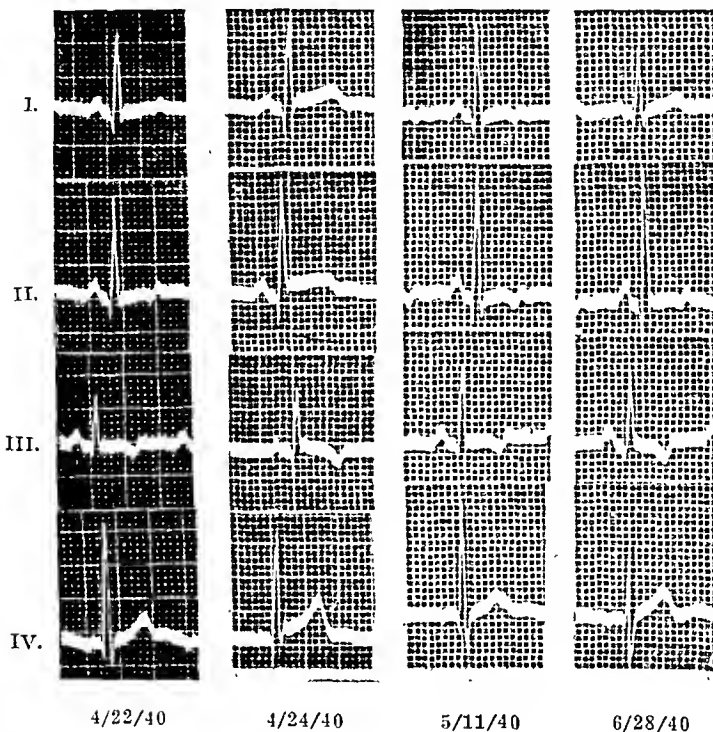


Fig. 10.—Sequence of electrocardiographic changes in Case 10.

The patient's physician made a provisional diagnosis of acute pericarditis, but, because of the obviously incongruous features of the attack, he wished our opinion on the electrocardiographic tracings, which are reproduced here.

The features which suggest pericarditis in the electrocardiographic tracings (Fig. 10) include the elevated R-T segments in the standard and precordial leads in the second tracing, the subsequent negativity of the T wave in the limb leads, and the tendency of the tracing to return to normal.

CASE 11.—The patient was a lawyer, aged 34 years, without history of previous illness. On Sept. 3, 1939, while he was driving, a dull intermittent, epigastric distress developed. This distress soon involved the lower part of the chest and an hour later became agonizing, with associated pain in the back of the neck. The pain was made worse by deep breathing. The patient was seen by his physician, who observed him, after two hours of severe pain, in apparent shock, and recorded a pulse rate of 110 and a temperature of 101.4° F. He was suspected of having coronary occlusion, was given 0.5 grain (0.032 Gm.) of morphine sulfate, and was moved by ambulance to the hospital. No history of friction rub was obtained.

The distress soon disappeared, and the patient wished to return home on the following day but was persuaded to rest in bed for six weeks. After this he felt

well and pursued an active life. On Jan. 21, 1940, he had pain across the lower part of his chest, was given 0.25 grain (0.016 Gm.) of morphine, and was kept in bed for one week. For the next two months there were occasional twinges of precordial pain and a sense of oppression in the left side of the chest when the patient was lying on the left side. He visited the clinic on March 6, 1940, where the results of general physical examination were negative; the blood pressure was 112/80. The electrocardiogram and the roentgenogram of the chest were normal. The patient returned to his normal life and full-time work, feeling well. When last heard from, in April, 1941, he had had no symptoms other than an occasional, fleeting, precordial discomfort.

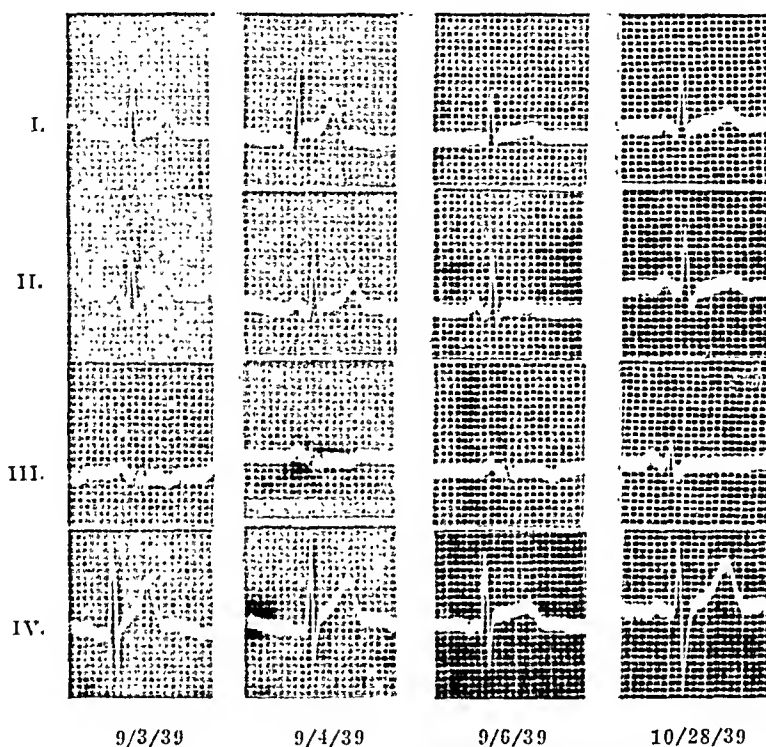


Fig. 11.—Sequence of electrocardiographic changes in Case 11.

The diagnosis of previous pericarditis rested almost wholly on our interpretation of the serial electrocardiograms which were taken after his attack of severe pain (Fig. 11). The elevation of the S-T segment in Leads I and II, with a convexity downward, accompanied by rather peaked T waves without any depression of the segment in Lead III, is believed to be indicative of some type of pericardial involvement. The electrocardiogram returned to normal within a few days, without anything to suggest a Q or T pattern of coronary occlusion. There was a questionable, slight diminution in the amplitude of the QRS complexes, and, in the third tracing, there was a dome-shaped T wave.

Three cases of pain in the chest suggested coronary occlusion; the correct diagnosis is believed to be acute pericarditis, but an associated coronary occlusion has not been absolutely excluded.

CASE 12.—A traveling salesman, aged 45 years, had had good health previous to his present illness, except for a mild illness in 1936 which lasted several months and was said to be accompanied by low-grade fever and some pleuritic pains.

On June 6, 1940, while he was driving, an aching pain developed in the right anterior part of the chest and extended into the right arm. The pain subsided but

recurred intermittently over the next week. When he was seen by his physician on June 10, examination gave negative results except for evidence of apprehension. The temperature was normal, and the leucocytes numbered 17,300 in each cubic millimeter of blood. The patient rested during the next six weeks and had only occasional pain in the right side of the chest. The blood pressure remained in the vicinity of 125/85 during this period. When he returned to work, August 1, he was still having occasional pain in the anterior part of the chest which came on with exercise and extended at times to both wrists; also, at times, he had a little "uneasiness" in the left wrist. On August 8, after his evening meal, more severe distress developed in the anterior part of the chest than he had experienced previously, and he vomited. On the following day the cardiac sounds were normal; the blood pressure was 98/76; and the temperature was 99.2° F. Hypodermic injections were given for relief of pain. Since then the patient has had recurring pain which begins in the right axillary region and spreads to the upper sternal region and arm. The pain occasionally lasts for hours, and the relief by rest has been indefinite.

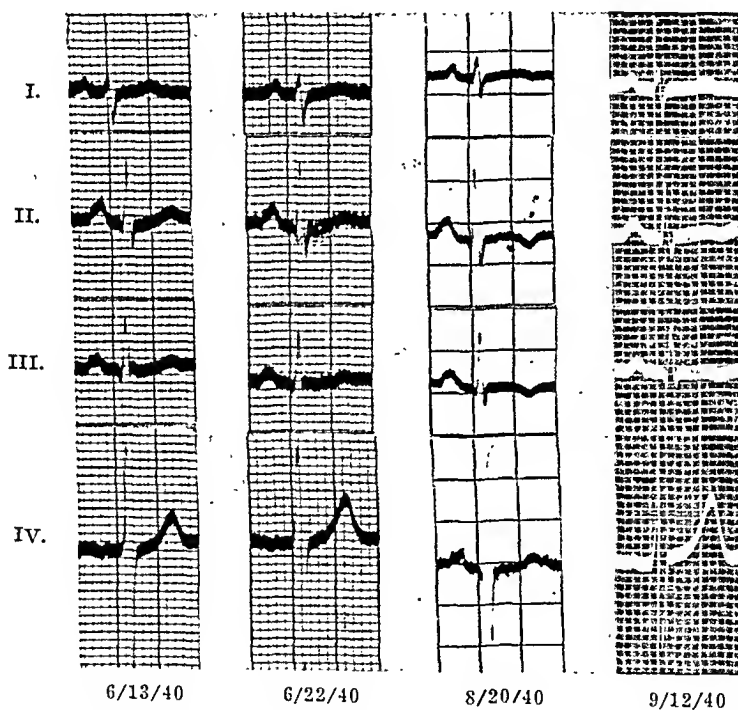


Fig. 12.—Sequence of electrocardiographic changes in Case 12.

In August, 1940, the patient was seen at the clinic, where the physical examination gave negative results; the blood pressure was 130/90, and the temperature was 99.2° F. The routine examination of the urine and blood and a roentgenogram of the chest showed nothing abnormal. The patient was encouraged to believe that he might not have coronary disease, and within a few weeks he had regained his normal health. When last heard from, in July, 1941, he was active, feeling well, and had had no pain in the chest for months.

The series of electrocardiograms (Fig. 12) did not show any abnormality during the early period of his illness. Later, negative T waves in Leads II and III and diphaseic T waves in Lead I developed. These tracings are not of great diagnostic help but are believed to be compatible with the diagnosis of pericarditis.

CASE 13.—A farmer, aged 46 years, registered at the clinic in July, 1940, complaining of epigastric distress which was of two months' duration, a dull pain over the precordial region, and some exertional dyspnea of three weeks' duration. On a number of occasions in previous years he had been seen at the clinic for minor complaints, such as hay fever and furunculosis, and the results of previous examination of the cardiovascular system had been negative. The precordial pain was described as not extending to other regions, as continuing over a period of several days, and as not being accentuated by exertion. There was also the history of a paroxysm of irregular heart action, which suggested auricular fibrillation. On

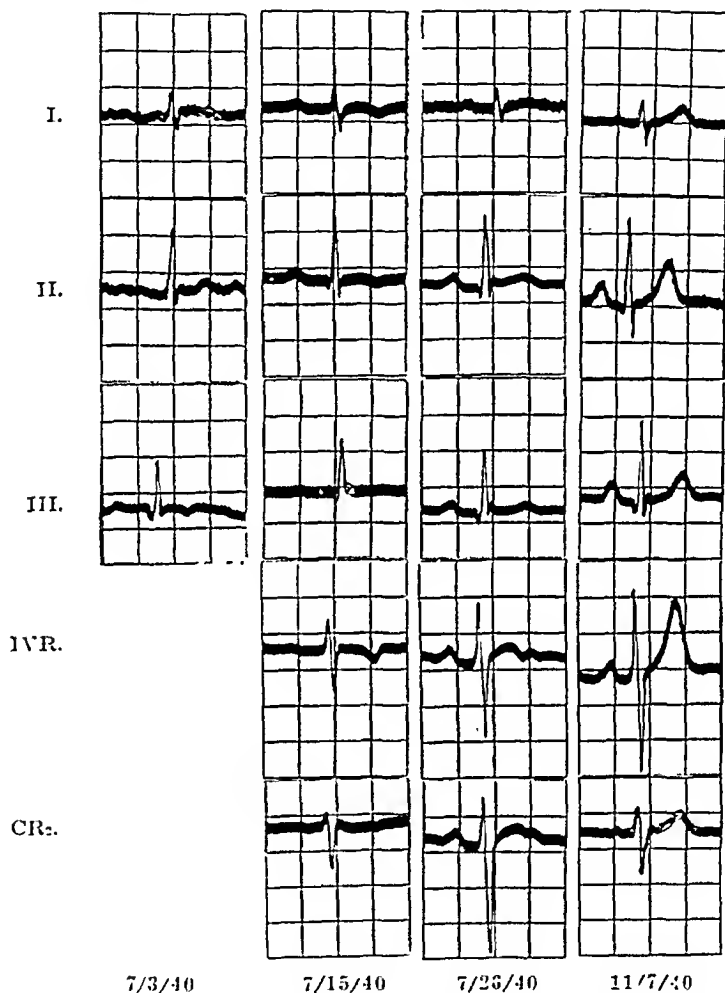


Fig. 13.—Sequence of electrocardiographic changes in Case 13.

physical examination the general condition of the patient seemed good, but there were a pericardial friction rub, slight enlargement of the liver, and moderate enlargement of the cardiac shadow. He was observed in the hospital for four weeks, during the first week of which there were low-grade fever, with temperatures up to  $103^{\circ}$  F., and an increased sedimentation rate (to 103 mm. in one hour). There was never any leucocytosis. Whether the pathologic process was acute pericarditis or coronary occlusion associated with pericarditis was uncertain for some time, but the rapid improvement of the patient and the sequence of events in the electrocardiograms firmly established the diagnosis of pericarditis, in our opinion. The patient was dismissed feeling well, and, when he was seen again in November, 1940, his cardiac status was considered to be that of a normal person. In July, 1941, he was feeling well and working full time in the harvest fields.

The electrocardiograms (Fig. 13) showed elevation of the S-T segment in the early tracing, followed by negativity of the T wave in subsequent tracings, but, interestingly, there was a second phase of elevation of the S-T segment, with dome-shaped T waves. The complete return of the tracing to normal occurred in three months' time.

CASE 14.—A woman, aged 60 years, whose past medical history was not noteworthy, other than for cholecystectomy, was seen at the clinic in December, 1923. In October, 1923, a sense of pressure had developed in the chest, with severe pain down the arms which lasted about an hour, and which was associated with nausea and diarrhea. There was mild pain in the anterior part of the chest for the following five days, and the home physician made a diagnosis of pericarditis. On examination at the clinic two months later, the patient was feeling fairly well and had only slight dyspnea on occasion. A diagnosis of coronary sclerosis and previous coronary occlusion, with myocardial infarction, was made. The outstanding feature of the electrocardiogram was negativity of the T waves in all three leads. When the patient returned to the clinic in 1924 and 1926, she gave a history of no further chest pain and no dyspnea. In March, 1941, her attending physician wrote that she was feeling well, although she was having increasing shortness of breath and edema of the ankles.

It may be questioned whether we are justified in including this case, as it may represent only a long survival after acute occlusion. However, the suggestive electrocardiographic tracing, together with the long history of freedom from pain in the chest, tempts us to believe that the attack of pain in the chest in 1923 might have been due entirely to acute pericarditis.

#### COMMENT

We do not assume that these patients had identical pathologic processes, but we do believe that in each case we were dealing with pericarditis, probably inflammatory in nature and infectious in origin. In support of the latter view was the history of a recent antecedent infection in many of the cases. Although the correct diagnosis in the cases here presented depended, we believe, chiefly on the correct interpretation of the associated electrocardiographic changes, there were numerous clinical characteristics of importance in the differential diagnosis. It is well known that inflammatory diseases of the pericardium may be completely painless, but it is in a small group of patients with pain sufficiently severe to suggest the possibility of coronary occlusion that we are particularly interested. The question whether, in some of these cases, there might have been evidences of rheumatic fever may be raised, but we consider this an unlikely possibility. Neither do we believe that these patients had a tuberculous process, although we occasionally have observed young adults with a benign, apparently self-limited form of pericarditis which may possibly have been caused by tuberculosis. None of the patients reported in this series had any evidence of an active focus of tuberculosis in the chest or lymph nodes or previous illnesses of a tuberculous nature.

It is a question whether these patients will have further recurrences of pericarditis, and whether constrictive pericarditis may develop. The former we consider possible in some instances, but the latter is unlikely.

In two cases, the type of pain was similar to that of the patients with spontaneous mediastinal emphysema reported by Scott<sup>1</sup> and by Hamman,<sup>2</sup> but, since the series of electrocardiographic tracings were so characteristic of pericarditis, we believe that the latter is more likely. These two cases were different from the group in general because of the absence of preceding infection, the intense severity but short duration of the pain, the absence of fever, rub, or cardiac enlargement, and the rapid return to health without any further distress in the chest.

*Clinical Features of Acute Pericarditis in Adults.*—The age incidence in the group of patients presented extends over a very wide range but tends to average lower than for patients with coronary occlusion. Averages may be misleading, but the average age of patients who have coronary occlusion is about 55 years, as compared with 42 years in our group of patients.

As previously mentioned, there was a history of some acute infection, usually in the upper part of the respiratory tract, preceding the attack of pain in the chest in 57 per cent of these cases. Of the first group of nine cases, in which the diagnosis seems established, preceding infection was present in all but one. Such a frequency of preceding acute infection is not observed among patients suffering from attacks of coronary thrombosis.

The pain in acute pericarditis shows certain differences from that of acute coronary thrombosis. It is seldom described as agonizing, is in general less severe, and less often requires morphine for relief. It is frequently intermittent, and there may be short premonitory paroxysms, unrelated to exertion, preceding the attack of severe pain which forces the patient to request medical care. The pain usually is located in the substernal and epigastric regions, but, in a few instances, it has been localized curiously over a small precordial area well to the left of the midline. The pain rarely extends to other regions, but, in some instances, there may be unilateral or bilateral pain in the shoulder tip, or diffuse pains in the sides of the chest and back. Deep breathing, rotation of the trunk, or swallowing may aggravate the pain. In some instances the history indicated that the patient was most comfortable in the sitting position, leaning forward. Although exertion may produce the pain, frequently it will be found to be due to flexion or twisting of the trunk, and the distress may persist for hours after the exertion ceases. Long after recovery from the acute phase of the disease, the patient may experience attacks of pain in the chest of variable location and duration, without reference to exertion.

Febrile reactions, in which the temperature reaches 101° F. or more, are much more likely to occur with infectious pericarditis than with myocardial infarction. Sharp febrile reactions, particularly if they respond rapidly to treatment with sulfonamide drugs, as in Case 1, speak for an infectious origin of the pericardial reaction.

In some cases of pericarditis the cardiac silhouette may be increased considerably in size. Such degrees of cardiac enlargement are unusual in acute myocardial infarction. Consequently, if a huge cardiac silhouette is observed roentgenographically, it favors the diagnosis of pericarditis rather than that of coronary occlusion. In the majority of these cases in which pain has been the outstanding feature, there has been little or no enlargement of the cardiac shadow, but in three cases there was moderate enlargement, with a return to normal when the patient recovered.

In the cases which we have been able to follow very closely, the sedimentation rate frequently has been an index of the presence of an infection, and only rarely has there been any elevation of the leucocyte count. Other laboratory examinations usually gave negative results.

*Electrocardiographic Features of Acute Pericarditis.*—The electrocardiographic distinction between acute pericarditis and acute coronary occlusion depends on two things. First, it implies complete familiarity with the pattern of changes in the standard and precordial leads which are produced by myocardial infarctions in various locations. Of course, it must be admitted that infarctions of unusual location or size, or multiple infarctions, occasionally produce electrocardiographic changes that cannot be classified. Second, it is necessary to understand the various general patterns of electrocardiographic changes that are produced by acute and subacute pericarditis.

The  $Q_1$ - $T_1$  and  $Q_3$ - $T_3$  changes in anterior and posterior infarction of the left ventricle are well known<sup>3</sup> and need no comment. We recognize many variations from these patterns which, if they occur in a serial manner after an attack of pain in the chest, will support a diagnosis of coronary occlusion. The electrocardiographic changes described by Wood and his associates<sup>4</sup> in infarction of the lateral wall may become established, in time, as another characteristic pattern.

Experimental and clinical evidence indicates that one of the most characteristic modifications of the electrocardiogram produced by pericarditis is upward displacement of the RS-T segments in the standard leads.<sup>5-9</sup> This is most characteristic if elevation occurs in all of the standard leads, although it may occur in Leads I and II, or almost exclusively in Lead I. The R-T of the elevated segment either is concave upward or forms a straight line from its origin in the R wave to the crest of the T wave. This is to be contrasted with the upward convexity of the elevated R-T segment in coronary occlusion. Reciprocal deviations of RS-T segments in Leads I and III, such as may occur after acute coronary occlusion, rarely occur in uncomplicated pericarditis. The T waves in acute pericarditis primarily tend to undergo one of two changes; they may become exaggerated in amplitude or sharply peaked, or they may be rounded, with a dome shape.



Very shortly the segment displacement is diminished or disappears altogether, and negativity of the T wave appears. In most instances, if frequent electrocardiograms are taken, there is a stage in which the T waves become negative in all of the standard leads. This in itself is suggestive of pericarditis, although it may be seen after acute coronary occlusion or after a second acute coronary occlusion. In the latter cases, the T waves usually have a shape which suggests coronary disease; the QRS often is deformed, particularly by notching; and the precordial lead may exhibit changes indicative of coronary occlusion.

The changes in the apical precordial lead are more difficult to classify. The S-T segment may duplicate the elevation observed in S-T<sub>1</sub>, but this is not common. The T wave in this lead may become exaggerated and sharp. At the stage of inversion of the T wave in the standard leads the T wave in IVR and IVF usually is inverted, although it may only lose voltage. Rarely is the R wave less than 2 mm., and usually it is of normal size, which assists in the exclusion of anterior infarction of the left ventricle. In no instance has a Q wave in the apical lead appeared in known acute pericarditis.

In acute pericarditis, Q and T patterns, such as occur in early or late myocardial infarction, are not observed. Loss of R in the apical lead and the appearance of a large Q in this lead, which changes are frequently associated with anterior infarction of the left ventricle, do not occur.

Occasionally (Case 8) the pericarditis appears to be more of a chronic or subacute variety, in which case low voltage of the QRS and T waves is the striking abnormality of the electrocardiogram. As recovery occurs, improvement in voltage is one of the first signs of electrocardiographic change. Under such circumstances, minor electrocardiographic changes may persist for weeks or months after the patient has regained his normal health.

Within one to six weeks after the more acute phase of pericarditis subsides, the electrocardiogram returns to normal or begins to approach normal limits. There are no traces of the Q or T pattern in the standard leads and no persistence of Q or absence of R in the precordial apical leads to suggest a previous occlusion. Aside from this lack of residue of acute myocardial infarction, this tendency to a rapid return toward normal is one of the most important features of the electrocardiogram in acute pericarditis and distinguishes it from that of coronary occlusion, which tends to be reflected by recognizable changes for a much longer period. This also emphasizes the great importance of a series of electrocardiograms in arriving at the correct diagnosis.

There remains the differentiation between acute pericarditis and coronary occlusion complicated by pericarditis. The distinction usually can be made because coronary occlusion, even though it may be complicated by pericarditis, will reveal itself by T or Q patterns in the

standard leads or by the appearance of a large Q wave or the absence of an R wave in the apical precordial leads.

It is to be emphasized that this is a select group of patients with a disease which is rare in comparison with the number of patients we have seen who had coronary occlusion within the same period. The outlook for these patients is entirely different, we believe, from that of patients with coronary disease. The decision that a patient has acute coronary thrombosis imposes a grave immediate prognosis, a guarded ultimate prognosis, a prolonged convalescence, and a permanent modification of the patient's way of living. A diagnosis of acute pericarditis warrants a good immediate and remote prognosis and a period of convalescence less prolonged, on the average, than that demanded by acute coronary thrombosis, and allows the patient to resume his normal life after recovery from the attack.

#### SUMMARY

Fourteen cases are presented, together with evidence which we believe justifies a diagnosis of acute infectious pericarditis, rather than acute coronary occlusion. Because of the nature and location of the pain, coronary occlusion had to be considered. In several instances in which a friction rub was heard, the natural inclination was to make a diagnosis of acute pericarditis, until the electrocardiographic changes confused the issue. The clinical and electrocardiographic grounds on which we have concluded that the correct diagnosis in each of these cases was acute infectious pericarditis have been stated.

In these cases the disease uniformly ran a benign course, with good recovery and without any evidence of significant impairment of cardiac function. Time alone will tell whether, in any of these cases, the disease will go on to the development of constrictive pericarditis, although we do not believe that it will. We have not found it necessary to impose any restriction on the normal activity of these people after the lapse of the few weeks to two or three months which were required for recovery. The indefinite pain in the chest which was observed occasionally in these persons subsequent to their acute attacks has not been accompanied by any demonstrable cardiac abnormality, has not been productive of any signs of myocardial insufficiency, and does not appear to nullify the good prognosis given to these patients.

Although none of these diagnoses was verified by post-mortem studies, the observations on the characteristics of the electrocardiographic changes which are seen in pericarditis are based on the results of investigations on pericarditis in animals and in other cases of pericarditis in man in which post-mortem studies were made.

It is our belief that this is an important problem. If our thesis is correct, there must be occasional instances in daily practice in which a lack of appreciation of the distinctions made here results in mistaking acute pericarditis for acute coronary occlusion. It is of the utmost

importance that such a mistake be avoided, because the immediate and ultimate prognosis and the program of future restrictions in the two conditions are so utterly different that great injustice to the patient may result from failure to make the correct diagnosis.

We have many acknowledgments to make to physicians who cooperated with us by sending electrocardiograms and details of the illnesses of many of these patients. We must mention, in particular, the following: Dr. Young, Duluth, Minn.; Dr. Hiett and Dr. Howell, Fort Worth, Texas; Dr. Kurtz and Dr. Lustok, Milwaukee, Wis.; Dr. Seherer and Dr. Fahr, Minneapolis, Minn.; Dr. Nickel, Bluffton, Ind.; Dr. Matthews, Shreveport, La.; Dr. Berger, Cleveland, Ohio; and Dr. Langston, Oklahoma City, Okla.

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#### DISCUSSION

DR. GEORGE HERRMANN, Galveston, Texas.—The diagnostic electrocardiographic patterns worked out by Dr. Barnes are indeed very important, but require expert interpretation. The clinical diagnosis, even with the electrocardiographic studies, is not always as easy as one might think from his presentation. Some of us have seen cases in which a diagnosis of acute pericarditis was made, and later evidence developed which showed definitely that the acute pericarditis was really pericarditis epistemonocardia. This was of particular importance in two cases in which pericardiectomy was contemplated, but in which, fortunately for the surgeon, death came suddenly on the eve of the operation; autopsy revealed that the abnormal pericardium was adherent to the thin scar of ventricular aneurysm. That impressed me with the fact that we must not go to the other extreme and make a diagnosis of simple pericarditis in instances in which pericarditis epistemonocardia has developed. This must be kept in mind when patients have constrictive symptoms for the relief of which cardiac decortication is being considered.

DR. AARON ARKIN, Chicago.—We not infrequently see, in the hospital, young patients with acute pericarditis. A large percentage of the cases are tuberculous in nature. The diagnosis is not difficult when rheumatic heart disease can be excluded. These patients have an enlarged heart shadow which often recedes rapidly after a few weeks of bed rest. Roentgenologic examination often reveals a definite enlargement of the hilar lymph nodes, occasionally with some calcification.

This kind of collateral inflammatory tuberculous pericarditis is not serious and is caused by the close contact of a tuberculous lymph node with the pericardium.

The patient, usually a young person, complains of cardiac pain. Dyspnea may or may not be present. In the early stage a pericardial rub may be found. The heart shadow is often greatly enlarged by the effusion, which may be serous, sero-fibrinous, or hemorrhagic.

I do not believe that we should confuse these cases with those of acute coronary occlusion. The patients have few or no symptoms, sometimes not even dyspnea. One is astonished to find the enlarged area of dullness which shifts at the base with change of position. The electrocardiogram shows the usual changes which are caused by pericarditis.

The lymph nodes in contact with the pericardium may also cause an associated pleural effusion. The prognosis is good. Such a pericardial effusion, which is often without tubercle formation, is not a serious disease. In a few weeks the cardiac shadow may return to normal.

DR. JOSEPH B. VANDER VEER, Philadelphia.—We have had experiences at the Pennsylvania Hospital which are rather similar to those of Dr. Barnes and agree that this disease is not infrequently mistaken (from the electrocardiographic standpoint) for myocardial infarction. During the past few months we have seen three patients whose electrocardiographic changes had been interpreted as being due to myocardial infarction, but careful analysis of the record suggested that they were caused by acute pericarditis. This was subsequently borne out by other records and the clinical course of the patients.

One thing Dr. Barnes did not stress is that hemopericardium frequently produces the electrocardiographic pattern of acute pericarditis. The inflammation produced by the blood extends to the subepicardial myocardium in different areas of the ventricles and gives rise to the elevated RS-T segments. We have seen two patients of this type. At autopsy one of them, a youngster about 18 years of age with an unrecognized congenital lesion of the aorta, had a small rupture, with hemopericardium, although death did not occur for several days. The other patient had an aortic aneurysm, with oozing of blood into the pericardial sac for several days before the final rupture.

Our results in pericarditis bear out Dr. Deeds' observations on the chest leads. There is no one precordial lead that is best for all conditions. (Slide) I believe this slide illustrates well the variations one may get in the chest leads. It is typical of acute pericarditis. There are elevations of the RS-T segments in all of the CR leads, most marked in CR<sub>1</sub> and CR<sub>2</sub>. The CF leads, however, show no significant changes, and Lead V (Wolferth and Wood) and Lead IVB show no changes. CL leads were also done and were similar to the CF leads in this case.

So, in this instance again, although the limb leads may be sufficient, it is helpful to have changes in the chest lead which may aid in confirming the diagnosis.

DR. LOUIS N. KATZ, Chicago.—In 1928, Dr. R. W. Scott, Dr. Harold Feil, and I were the first to describe this typical electrocardiographic pattern in a case of hemopericardium. Two years ago, Dr. R. Langendorf, of Prague, came to work at the Michael Reese Hospital and renewed my interest in the subject because he was enthusiastic about the studies he and his colleagues had made on this electrocardiographic feature. They had described, independently of Barnes, a similar electrocardiographic pattern in pericarditis. Since Dr. Langendorf has been with me, we have seen about half a dozen cases in which the characteristic electrocardiographic changes were present. The clinical manifestations noted by Dr. Barnes were also present in our cases.

DR. MAURICE S. JACOBS, Philadelphia.—One of the points that Dr. Barnes mentioned, but did not stress, was the character of the pericardial friction rub—not so much the character as the length of time that it lasts. It has been our impression that the pericardial friction rub, as it occurs in acute myocardial infarction, is of short duration. In short, in myocardial infarction one frequently does not hear a pericardial friction rub. It has been our opinion that this is due to the fact that the patient is not examined often enough. By that I mean not just once a day, but sometimes three or four times a day. One frequently hears a pericardial friction rub, for example, at seven o'clock at night which was not there in the afternoon or might not be there at midnight.

Ten years ago we pointed that out in a case of acute myocardial infarction in which, the third day after that infarction, the pericardial friction rub appeared at about seven o'clock at night and was gone by midnight. The patient had been examined twice before that day. I believe this is something that ought to be kept in mind.

DR. ARLIE R. BARNES, Rochester, Minn.—I subscribe to what Dr. Herrmann has said, namely, that we must not become overenthusiastic about pericarditis, but still I believe that we have been too prone to diagnose coronary thrombosis without sufficient consideration of other possibilities.

I was interested in what Dr. Arkin had to say about tuberculous pericarditis. We have seen it occasionally, but not in patients as old as those in this group.

Dr. Burchell and I had an interesting discussion concerning heart size. I have seen many cases of pericarditis in which the heart became large very rapidly, and I am convinced that in some of these cases we are dealing with the finest examples of acute dilatation of the heart which are known to clinical medicine. The enlargement is ordinarily ascribed to the accumulation of fluid in the pericardial sac, but I have had occasion to tap the pericardial sac as many as three times without obtaining any fluid whatsoever. Therefore, I believe that dilatation of the heart may occasionally be an important feature of acute pericarditis.

We have had the same experience as Dr. Vander Veer, namely, that hemopericardium will produce the same electrocardiographic changes that we have just described.

I am grateful to Dr. Jacobs for mentioning the duration of the friction rub, for it is true that in cases of pericarditis the rub persists for days, and sometimes as long as two weeks, whereas it may be transitory in acute myocardial infarction. In the making of the differential diagnosis, the electrocardiogram becomes the final arbiter, and one must be able to distinguish between the electrocardiographic mutations in pericarditis and those in acute coronary occlusion.

## Department of Clinical Reports

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### SINOAURICULAR BLOCK AND RETROGRADE AURICULAR CONDUCTION IN A CASE OF PERMANENT COMPLETE HEART BLOCK

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CASES of obvious sinoauricular block have seldom been recorded, although some authors state that they are probably more frequent than is supposed.<sup>1-6</sup> However, medical literature does not contain any instance in which sinoauricular block was associated with permanent complete heart block. For this reason we wish to record such a case.

In 1902, Mackenzie<sup>7</sup> first suggested that such a thing as sinoauricular block may occur, and, in 1907, Wenckebach<sup>8</sup> first described it fully. Levine<sup>1</sup> reported eighteen cases up to 1916, and Barlow<sup>9</sup> collected thirty-six between 1916 and 1926. Sinoauricular block may be caused by a disturbance in the node produced by humoral or nervous influences, or it may result from an organic disorder. No complete histologic study of the sinoauricular node has been made in any of these cases.

Included among those who believe that sinoauricular block is a functional disturbance is Smith,<sup>2</sup> who reported eight children with this condition. Of these, six were convalescent from diphtheria, whooping cough, or mumps. Zárday<sup>10</sup> described two cases, in one of which there was a brain tumor; in the other there was a Wenckebach block of both the sinoauricular node and the auriculoventricular node. Barlow<sup>9</sup> recognized the frequent association of sinoauricular block with a prolonged P-R interval. He could find no definite etiology, but implicated such factors as digitalis, salicylates, tobacco, infections, coronary sclerosis, and rheumatic heart disease. He noted that atropine usually abolished the block temporarily and concluded by saying that sinoauricular block was a "physiological" disturbance. Feldman<sup>11</sup> reported the case of a man with syphilitic heart disease and aortic insufficiency who had a prolonged P-R interval and occasional sinoauricular block. The latter increased after right carotid sinus stimulation and disappeared after the administration of  $\frac{1}{75}$  grain of atropine sulfate.

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Against the above opinion are the statements of Levine,<sup>1</sup> White,<sup>3</sup> Lewis,<sup>4</sup> Wallace and Katz,<sup>5</sup> and Van Buchem,<sup>12</sup> who look upon sinoauricular block as "pathological." They stress the fact that, in a majority of the cases which have been reported, there was evidence of arteriosclerotic, rheumatic, or syphilitic heart disease, a history of convalescence from a severe infection, the presence of defective auriculoventricular conduction, or previous administration of digitalis. Wallace and Katz<sup>5</sup> reported a case of sinoauricular block in which there was not only prolongation of the P-R interval, but also occasional dropping of a ventricular beat.

#### CASE REPORT

J. G., a 64-year-old white man, was admitted to the service of Dr. I. W. Held, at Beth Israel Hospital, on Dec. 19, 1939, because of the sudden onset, two weeks prior to admission, of dizziness and substernal pain which lasted two minutes. Several hours later, while walking home, the patient experienced vertigo, followed by unconsciousness for about three minutes. There were no symptoms thereafter until three days before entry, when he became dizzy and vomited several times. For the preceding two years he had experienced moderate dyspnea, and an aching substernal pain, which occasionally radiated to the left shoulder, was induced by exertion, and was relieved by one to two minutes' rest. There had been no orthopnea, nocturnal dyspnea, palpitation, edema of the ankles, or known hypertension. There was no history of syphilis. An electrocardiogram, taken at home the day preceding admission, showed complete heart block.

Physical examination revealed a well-nourished and well-developed elderly man who was slightly cyanotic but not dyspneic. The patient was alert, oriented, and cooperative. The neck veins were not distended. The pupils were equal and regular and reacted well. The optic discs were well outlined; the retinal veins were full and tortuous; and the arteries were thin. The lungs were normal. The apex impulse of the heart could not be felt. The rhythm was regular. The ventricular and pulse rates were 30 per minute. The sounds at the base of the heart were barely audible, but at the apex they were of fair quality. There were no murmurs. The blood pressure was 120/54. The liver was felt 2 to 3 fingerbreadths below the costal margin. The spleen was not felt. There was no peripheral edema. Bilateral inguinal hernias were present. The prostate was slightly enlarged but was smooth.

*Laboratory Data.*—The specific gravity of the urine was 1.010 to 1.018; the urine contained a trace of albumin, and an occasional cast and leucocyte. On admission, the erythrocyte count was 5,210,000; the hemoglobin, 105 per cent (Sahli); and the leucocyte count, 14,300, with 79 per cent polymorphonuclear cells. The sedimentation rate was 4 mm. in forty-five minutes. The venous pressure was 14 cm. of blood. The blood Wassermann, Kline, and Kahn reactions were negative. The blood glucose was 105 mg. per cent, and the nonprotein nitrogen was 120 mg. per cent.

*Course.*—A diagnosis of arteriosclerotic heart disease with complete heart block and Morgagni-Adams-Stokes syndrome was made. The pulse rate varied between 22 and 32, without therapy. Movement in bed caused dizziness and weakness; nausea was constant. Adrenalin increased the pulse rate and lessened the symptoms. The patient's illness was complicated on the sixth day in the hospital by a massive hematemesis, probably from a peptic ulcer. During the twentieth and twenty-first days in the hospital, Jan. 7 and 8, 1940, he had several severe attacks of Morgagni-Adams-Stokes syndrome, with convulsions and unconsciousness, asso-

ciated with ventricular standstill for seven to ten seconds. Adrenalin, given hypodermically, produced relief. On the twenty-second day the patient had an acute perforation of a gastric ulcer, for which laparotomy and simple closure were performed. The patient was fully digitalized with digifolin intramuscularly because of signs of early congestive failure. His postoperative condition was never good. The heart rate was 44 per minute. The patient presented the clinical picture of peripheral circulatory collapse, with a blood pressure of 80/40. Death occurred suddenly on the second postoperative day.

*Principal Pathologic Observations.*—The outside configuration of the heart was normal. No endocardial lesions were seen. The coronary arteries, in general, were normal in size. The endocardium of the left ventricle was slightly opaque and thickened. A transverse incision 1.2 cm. below the base of the posterior aortic cusp, slightly behind its middle, revealed a somewhat butterfly-shaped scar which, in its posterior portion, was separated from the endocardium by a thin layer of myocardium which appeared grossly intact. A parallel incision 6 mm. below this one showed only traces of discoloration in the myocardium. In the lower portion of the left ventricular wall, a few grayish-white areas, up to 1 cm. in diameter, were seen. There seemed to be a number of much smaller ones. The wall of the left ventricle, halfway between base and apex, measured without the trabeculae, was 2.2 cm. thick; that of the right ventricle measured 3.5 mm. The right auricle, particularly in the region of the sinus node, showed nothing unusual. After continued fixation, an irregularly purplish field, measuring 1.1 cm. transversely and 0.9 cm. sagittally, became visible in the region of the sinoauricular node. It contained a small, round, darker, red spot. Longitudinal section of this region showed a corresponding subendocardial area which appeared more purplish and yellowish than the surrounding myocardium. The ascending aorta was slightly larger than normal; its intima was smooth.

*Microscopic Observations.*—No complete serial examination of the conducting system could be made. In the region of the large scar in the upper portion of the interventricular septum, fibrotic destruction of the septum was found. The destruction, in irregular fashion, permeated the whole thickness of the septum. In view of the fact that this large lesion must have severely affected either the lower part of the common trunk or the uppermost portions of the right and left branch of the bundle, it seemed reasonable to regard the multiple areas of subendocardial atrophy in both ventricles as a degenerative process in the ramifications of the bundle of His. Sections from the region of the sinoauricular node showed widespread atrophy and fibrosis of the muscular tissue which, perhaps, included damage to the node.

*Summary of Pathologic Observations.*—The pathologic changes were (1) moderate sclerosis of the coronary arteries (without narrowing of the major branches), (2) a scar in the upper portion of the interventricular septum, and (3) atrophy of the muscular tissue in the region of the sinoauricular node.

*Electrocardiographic Observations.*—Tracings were taken on ten different days. The following are the outstanding observations: (1) The A-V block was always complete, even on long tracings. (2) Sinoauricular block was present on five different days. This diagnosis was established by the occasional absence of a P wave in the presence of a fairly constant P-P interval ( $\pm 0.02$  sec.), and by the fact that the interval between the P wave preceding and the one following the dropped P wave was double the usual P-P distance (Fig. 1). (3) Inverted P waves were seen after certain idioventricular contractions on four different days. They were interpreted as retrograde auricular contractions similar to those previously recorded by Cohn and Fraser,<sup>13</sup> Wilson and Robinson,<sup>14</sup> Danielopolu and Danulesco,<sup>15</sup> Barker,<sup>16</sup> Wolferth and McMillan,<sup>17</sup> and Kline, et al.<sup>18a</sup> (Fig. 1).



## ANALYSIS OF OUR DATA ON SINOAURICULAR BLOCK

Analysis of the electrocardiograms revealed that the dropped P waves occurred only within an interval which extended grossly from the final deflection of the QRS complex to a point on the upswing of the T wave.

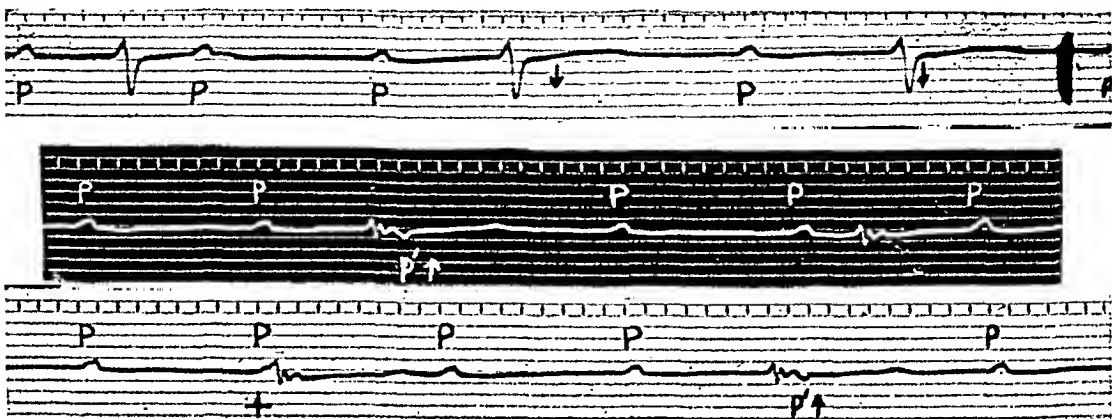


Fig. 1.—Tracing 1 (Dec. 28, 1939) shows S-A block after the second and third idioventricular beats. The arrows indicate the locations of the dropped P waves (R-P intervals of 0.30 sec. and 0.15 sec., respectively). The first idioventricular beat precedes the next P wave by 0.40 sec., and no S-A block takes place. The P wave is superimposed on the T wave. Time marked in 0.10 sec.

Tracings 2 and 3 are continuous (Jan. 7, 1940) and show retrograde auricular contractions (P) after the first and fourth idioventricular beats. The arrows mark the site of the normal sinus discharge.

P waves superimposed upon the QRS complex and the latter part of the T wave could be discerned readily (Fig. 1). The sinoauricular block in our case was not part of a Wenckebach period of the sinus node, because we were unable to detect any regular prolongation of the P-P interval preceeding the dropped P wave. Furthermore, the relationship of the sinoauricular block to the preceding idioventricular contraction was not a coincidence dependent upon a chance phasic rhythm between the auricles and ventricles, for the sinoauricular block was observed when the auricular rate varied between 60 and 91, and the ventricular rate, between 24 and 41. The invariable relation of the dropped beat to the idioventricular contraction led us to conclude that the latter was indirectly responsible for the appearance of sinoauricular block in this case. The most probable explanation is that there was a temporary increase in vagal tone associated with each ventricular systole. During the prolonged diastole of the ventricles the aortic pressure fell markedly; then the large stroke volume of each systole caused a sharp stimulation of the carotid sinns and aortic depressor nerves which resulted in an increase in the vagal tone and a decrease in sympathetic tone.<sup>18b</sup> Ashman and Gouaux<sup>19</sup> and Kisch<sup>20</sup> have shown that striking alterations in vagal tone do occur with each ventricular systole in cases of complete heart block.

The data from all of the electrocardiograms which were taken on five different days are summarized in Table I. When the R-P interval was 0.00 to 0.10 sec., sinoauricular block never occurred; when it was

0.11 to 0.12 sec., sinoauricular block appeared three out of seven times; when it was 0.13 to 0.39 sec., sinoauricular block always occurred; when it was 0.40 to 0.42 sec., sinoauricular block was seen only two out of thirteen times; and, finally, when it was 0.43 to 1.00 sec., sinoauricular block never occurred (111 instances). If a vagal reflex were an important factor in the block in our case, the latter should have

TABLE I

THE RELATIONSHIP OF THE R-P INTERVAL TO THE FREQUENCY OF OCCURRENCE OF S-A BLOCK

| R-P (SEC.) |               | 0.00-0.10 | 0.11-0.12 | 0.13-0.39 | 0.40-0.42 | 0.43-1.00 |
|------------|---------------|-----------|-----------|-----------|-----------|-----------|
| S-A block  | Present (no.) | 0         | 3         | 51        | 2         | 0         |
|            | Absent (no.)  | 11        | 4         | 0         | 11        | 111       |

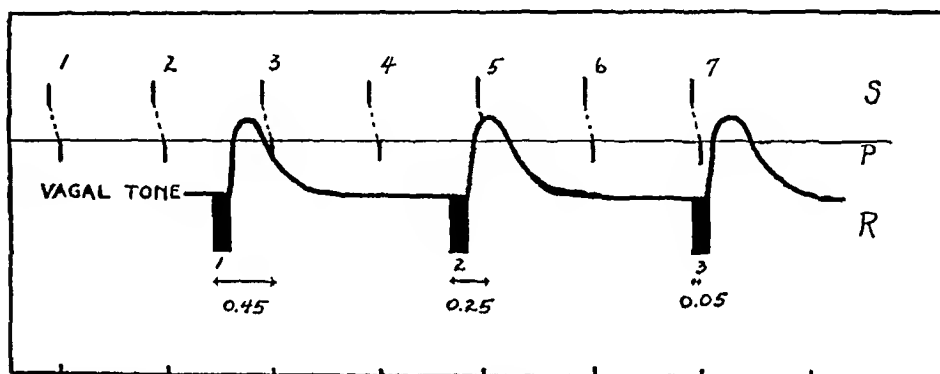


Fig. 2.—Diagram illustrating the relationship of idioventricular contractions to alterations in vagal tone and the occurrence of S-A block. Uppermost row of vertical lines indicates sinus impulse (*S*). The oblique dotted lines represent sinoauricular conduction (exaggerated for clarity). These end in vertical lines denoting auricular contraction (*P*), except at 5. *R*<sub>1</sub>, *R*<sub>2</sub> and *R*<sub>3</sub> represent QRS complexes upon which there is a curve depicting the change in vagal tone after each idioventricular beat. Note that this curve does not rise until the end of the QRS complex (0.11 sec. See text). The horizontal line above *P* represents the threshold of vagal tone above which S-A block occurs (duration, 0.26 sec.). When R-P is 0.45 sec., S-A block does not occur because vagal tone has just fallen below threshold. When R-P is 0.25 sec., S-A block does occur because vagal tone is at its height. An R-P of 0.05 sec. results in an elevated P-P = 0.80 sec. R-R = 1.80 sec.

coincided with the time of increased vagal tone. And so it did. The latent period between the beginning of the electrical effects of ventricular systole and the mechanical effect upon the aortic and sinus nerves is 0.11 sec., according to Ashman and Gouaux.<sup>19</sup> Another 0.01 sec. is required for the reflex arc to be completed. Therefore, 0.12 sec. after the initial deflection of the QRS complex one can expect a depression of the excitability of the sinoauricular tissue. In our case this effect was apparently sufficient to cause sinoauricular block whenever the R-P distance was between 0.13 sec. and 0.39 sec. When the R-P interval exceeded 0.42 sec., block never occurred, probably because by this time the vagal tension had subsided and was no longer sufficient to interfere with sinoauricular conductivity. Similarly, an R-P interval of less than 0.11 sec. was too short to produce a heightened vagal tone at the time of the normal sinus impulse. These facts are depicted graphically in Fig. 2.

Tracings taken Dec. 16 and 28, 1939, showed that after each idioventricular contraction there was also a slowing of the auricular rate, in addition to the specialized occurrence of sinoauricular block. This would indicate that the increase in vagal tone had both a chronotropic and dromotropic effect. On one occasion  $\frac{1}{15}$  grain of atropine sulfate was given hypodermically with no effect on the auricular rate or the sinoauricular block.

#### ANALYSIS OF OUR DATA ON RETROGRADE CONDUCTION

Inverted P waves after certain idioventricular contractions, representing retrograde auricular contractions, occurred in tracings taken on four different days. These were best seen in the Leads II and III. Fig. 1 illustrates this condition. P<sup>1</sup> designates the retrograde auricular contraction. The following observations are noteworthy:

1. The P-P interval varied between 0.71 and 0.90 sec. in all of our tracings.

2. The retrograde P waves appeared only in part of the second half of diastole of the auricles, namely, only where the preceding P-R interval was 0.40 to 0.76 sec. (Table II).

TABLE II

RELATIONSHIP OF THE PRECEDING P-R INTERVAL TO THE FREQUENCY OF OCCURRENCE OF RETROGRADE CONDUCTION

| P-R (SEC.)            |               | 0.00-0.39 | 0.40-0.47 | 0.48-0.71 | 0.72-0.76 | 0.77-0.88 |
|-----------------------|---------------|-----------|-----------|-----------|-----------|-----------|
| Retrograde conduction | Present (no.) | 0         | 7         | 46        | 6         | 0         |
|                       | Absent (no.)  | 62        | 8         | 0         | 5         | 4         |

3. The R-P<sup>1</sup> interval varied between 0.14 sec. and 0.20 sec. and was roughly inversely proportional to the length of the preceding P-R interval (Fig. 3).

4. The sum of P-P<sup>1</sup> and P<sup>1</sup>-P was equal to twice the usual P-P interval, and the P<sup>1</sup>-P distance exceeded the usual P-P interval by 0.02-0.28 sec. Therefore, there was a compensatory pause of the auricles.

The normal sinus rhythm in our case was not disturbed by the premature retrograde contraction of the auricles. This would be possible only if there were an auriculosinus block.<sup>21</sup> There was also sinoauricular block as a result of refractoriness of the auricle after the retrograde systole. Therefore, on these days there were both "entrance" and "exit" blocks around the sinoauricular node.

There are two possible mechanisms for the production of retrograde auricular contraction in a case of complete heart block. The first is mechanical stimulation of the irritable auricle<sup>13</sup> or A-V node<sup>14, 16</sup> by the impact of ventricular systole. The second is retrograde conduction of the impulse from the ventricle via intact conduction fibers within the scar, as suggested by Danielopolu and Danulesco<sup>15</sup> and Wolferth and McMillan.<sup>17</sup> In the present state of our knowledge, it can be said

that mechanical stimulation of the auricles is probably not the underlying cause. We feel that the more likely mechanism is either mechanical stimulation of the bundle of His or A-V node above the scar, or actual retrograde conduction through the area of block in the bundle of His. In our case it seems that the premature auricular contraction received its impulse from a focus in the conduction tissue, because (1) it always occurred late in the interauricular interval after the refractory period of the A-V tissue, (2) the P waves were always of the same contour, and (3) the R-P<sup>1</sup> interval varied directly with the duration of the recovery phase of the tissue, as measured by the preceding P-R interval.

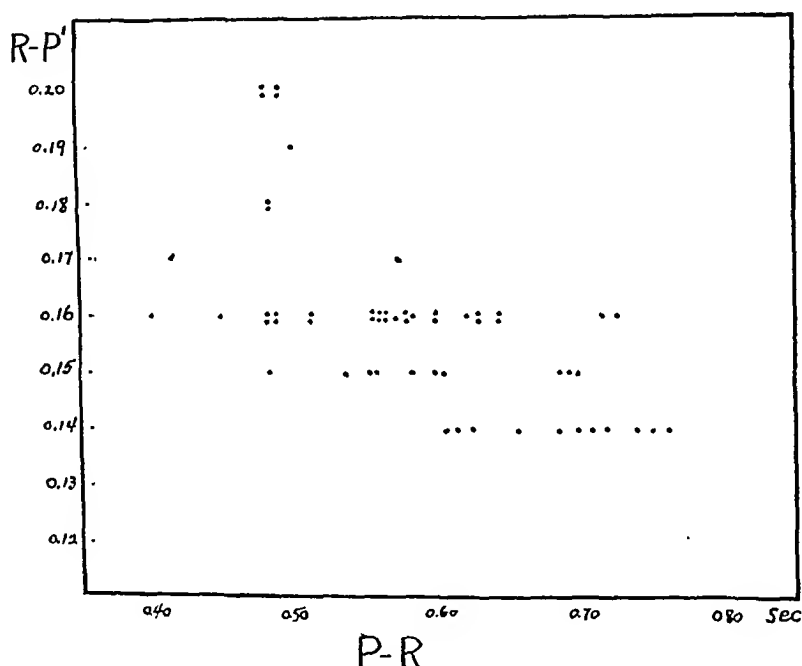


Fig. 3.—Scatter graph showing the inverse relationship between the retrograde conduction time (R-P<sup>1</sup>) and the length of the preceding P-R interval or recovery phase. This type of correlation resembles that seen with progressive recovery. On the other hand, in the supernormal phase of excitability, conduction time is shortest early, and longest late, in the recovery period.

The retrograde conduction appeared only when the P-R interval varied from 0.40 to 0.76 sec. These limits coincide closely with those reported by others as representing the supernormal phase. Kline, et al.,<sup>18a</sup> found it to be 0.32 to 0.65 sec. In cases of paroxysmal complete heart block, normal auriculoventricular conduction occurred when the Q-P interval was 0.425 to 0.708 sec.,<sup>22</sup> 0.31 to 0.795 sec.,<sup>23</sup> and 0.45 to 0.74 sec.<sup>24</sup> Nahum and Hoff<sup>25</sup> have ascertained the supernormal phase of the ventricular musculature of cats, dogs, and monkeys and found it to extend approximately from 0.40 to 0.64 sec. after the onset of the QRS complex. These limits correspond closely to those for the conduction tissue. However, the recovery curve of the conduction tissue in our case showed improving excitability with increasing recovery

(Fig. 3). This type of curve, with a late plateau, resembles the curve of progressive recovery, rather than that previously reported as being characteristic of a supernormal phase. Such curves, constructed from similar observations on man by Lewis and Master<sup>22</sup> and Ashman and Herrmann,<sup>23</sup> and also on bloodless turtle hearts,<sup>23</sup> show a rapid rise with an early peak, and then a gradual fall. Although our observations do not exclude the influence of a supernormal phase of the conductive system in the production of retrograde conduction, in our case we feel that progressive recovery of the conduction tissue adequately explains this phenomenon. The absence of retrograde conduction when P-R was above 0.76 sec. does not speak in favor of the importance of the supernormal phase in retrograde conduction but is sufficiently explained by the fact that a retrograde stimulus which came at this time reached the auricle too late to prevent an orthograde auricular contraction.

#### DISCUSSION

In our opinion, sinoauricular block is never a physiologic phenomenon. It is always due to more than one factor. In our case it was caused by a combination of myocardial fibrosis in the region of the sinoauricular node, increased vagal tension, and myocardial malnutrition secondary to coronary insufficiency. There was no relationship between digitalis and sinoauricular block or retrograde auricular conduction.

#### SUMMARY

1. A case of complete heart block with occasional sinoauricular block and retrograde auricular beats is presented.

2. The dropping of P waves occurred in a definite relation to the beginning of the preceding idioventricular contraction. The time of the sinoauricular block coincided with the time of the highest vagal tone after the idioventricular beats.

3. Retrograde P waves occurred only when the preceding P-R interval was 0.40 to 0.76 sec. Although that coincided with the supernormal phase in the auriculoventricular node or bundle of His above the scar, this phase probably played no important role in the retrograde conduction in our case.

4. The time of the retrograde conduction in our case bore a definite relation to the length of the preceding P-R interval. This may be expected to occur when the conduction tissue is damaged and the rate of conduction varies with the degree of its recovery.

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# Department of Reviews and Abstracts

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Herrick, J. F., Corcoran, A. C., and Essex, H. E.: The Effects of Renin and of Angiotonin on the Renal Blood Flow and Blood Pressure of the Dog. *Am. J. Physiol.* 135: 88, 1941.

Both renin and angiotonin decrease the blood flow in the renal artery and increase arterial pressure. In a few observations on the flow in the femoral artery it was found that both renin and angiotonin caused a diphasic effect consisting of an initial transient decrease followed by a somewhat more pronounced and prolonged increase. Pentobarbital sodium anesthesia did not seem to alter the hemodynamic effects of these substances.

AUTHORS.

Page, I. H., McSwain, B., Knapp, G. M., and Andrus, W. D.: The Origin of Renin-Activator. *Am. J. Physiol.* 135: 214, 1941.

The liver is the chief source of renin-activator, and its removal or damage by toxic substances in normal and hypertensive dogs reduces the renin-activator content of plasma and hence the pressor response to injected renin. The pressor response to angiotonin and the angiotonin-activator of blood remains unaffected by these procedures.

AUTHORS.

Rodbard, S.: The Effect of Nephrectomy on the Blood Pressure Response to Renin and Angiotonin. *Am. J. Physiol.* 135: 124, 1941.

The intensity and duration of the blood pressure response to renin is essentially the same before and after nephrectomy. In some animals, however, the duration of the response is somewhat increased following nephrectomy.

Renin has many properties which would suggest that it is closely related to the mechanism responsible for arterial hypertension of renal origin. Among these are the consistent presence of renin in kidney extracts, the reaction of renin with some of the constituents of the blood (renin-activator) to produce a new pressor material (angiotonin), and the reduction in intensity of response to renin seen in adrenalectomized animals. Nevertheless it appears that renin has not fulfilled one of the criteria necessary for the substance responsible for hypertension, since no consistent potentiation of the intensity or duration of the blood pressure response occurs after nephrectomy. The increase in duration of the response seen in some animals after nephrectomy is not of the magnitude predicted for the mediator of hypertension by our previous experiments.

The similarity in the blood pressure response to angiotonin before and after total nephrectomy suggests that the kidney is not responsible for the destruction or elimination of this substance.

AUTHOR.

Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: "Anoxemia Test." *J. A. M. A.* 117: 2113, 1941.

This study is based on 373 anoxemia tests performed on 137 persons during the past thirty-nine months. On all but seventeen patients the test was done at least twice; on some it was done as often as twenty times.

A positive reaction was not observed in any patient without cardiac disease or severe anemia.

A positive reaction may be regarded as a sign of coronary insufficiency; a negative reaction does not exclude disease of the coronary arteries.

The occurrence of pain during a test with a negative result, particularly if it appears during the first ten minutes of induced anoxemia, affords presumptive evidence of a diminished coronary reserve. Under these circumstances the patient should be observed carefully for further signs of coronary disease and managed conservatively.

The test is simple and safe. In the past four years it has been done 1,024 times on 442 persons. Unpleasant reactions have been observed forty-six times in thirty-six patients. But there have been no serious effects, and the course of the disease has not been affected unfavorably as the result of repeated tests.

The test is helpful in the differential diagnosis of conditions producing pain in the chest. When the reaction is positive, it serves to distinguish discomfort due to coronary insufficiency from that caused by other disorders. It is useful in following variations in the coronary reserve and therefore in appraising the efficiency of the coronary circulation at the time of its performance. Serial observations reflect, in a general way, the trend of the clinical course. The test does not furnish evidence which makes it possible to predict the future occurrence of coronary occlusion. It affords an index of the adequacy of the coronary blood flow within the undefined limits, but it yields no information as to the nature or extent of the pathologic lesions in the heart.

#### AUTHORS.

Parkinson, J., Papp, C., and Evans, W.: *The Electrocardiogram of the Stokes-Adams Attack.* *Brit. Heart J.* 3: 171, 1941.

Stokes-Adams disease is a name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these. During a Stokes-Adams attack from ventricular standstill the auricle continues to beat, whereas in cardiac syncope of other types there is, as a rule, total cardiac standstill. Cardiac syncope of neurogenic origin (e.g., ordinary fainting and ventricular standstill from disease affecting the vagus or carotid sinus) and cardiac syncope of myocardial origin without heart block (e.g., in nodal bradycardia and in paroxysmal ventricular tachycardia) are excluded by this definition, although there are borderline cases.

The cardiac mechanism of Stokes-Adams attacks was studied on electrocardiograms recorded during the period of unconsciousness in eight cases and in fifty-six reported cases. These fall into four groups or types and are tabulated according to the electrocardiographic basis of the attack. Group I (twenty-eight cases and five of this series) includes those with ventricular standstill alone. Group II (sixteen reported cases and two of this series) includes those with (a) low ventricular tachycardia and (b) high ventricular tachycardia and fibrillation, when either is followed by ventricular standstill. Group III (twelve reported cases and one of this series) includes those with high ventricular tachycardia and fibrillation without ventricular standstill. Group IV includes those rare cases with extreme bradycardia in heart block.



It is evident that ventricular standstill alone is not the only cardiac lapse that determines a Stokes-Adams attack. It is often due to ill action and not to inaction of the ventricle. Ventricular standstill is responsible for about 55 per cent; ventricular tachycardia (with or without ventricular fibrillation), followed by ventricular standstill, for 25 per cent; and ventricular tachycardia without ventricular standstill, for 20 per cent.

Ventricular standstill is sometimes consecutive to a rise in the auricular rate. As exertion or emotion so seldom determines ventricular standstill, this increase in the auricular rate probably originates locally in the auricle and not from any nervous influence.

During a short ventricular standstill (below twenty seconds), the auricle beats regularly, often at an increasing rate, and the persistence of P waves during the ventricular standstill is a feature distinguishing it from total standstill of cardiac syncope. During a long ventricular standstill (above twenty seconds), or when ventricular standstill is preceded by high ventricular tachycardia and fibrillation (Group II), the auricle may show slower, irregular, and ectopic P waves, auricular fibrillation and flutter, or it may even stop.

In a group with ventricular tachycardia, multiple and variable extrasystoles and varying bundle branch block complexes between the attacks are common, as might be expected. Low ventricular tachycardia (up to 160) does not produce unconsciousness, but it provokes the subsequent ventricular standstill that does produce it (Group IIa). High ventricular tachycardia and fibrillation (200-500) produce unconsciousness (Group III), and this may be prolonged by the subsequent ventricular standstill (Group IIb). The electrocardiogram of ventricular tachycardia is composed of regular deflections like bundle branch block, which at high rates merge into simple undulations; yet the term "ventricular flutter" need not be used, for the resemblance to auricular flutter is superficial.

Ventricular fibrillation is distinguished from ventricular tachycardia by its irregularity in both rate and form, although the rate per minute may be the same, higher, or even lower. High ventricular tachycardia easily passes into fibrillation, which ends with ventricular standstill or with gradual resumption of the basic rhythm through a period of low ventricular tachycardia or of varying extrasystolic complexes.

The essential basis of an attack can be decided only by an electrocardiogram. The prolongation of unconsciousness or its late onset in ventricular tachycardia and fibrillation cannot distinguish this group from that of ventricular standstill alone, because other factors may influence unconsciousness, e.g., the suddenness of the development of block or of the fall in rate, a rapid succession of attacks, and the state of the cerebral arteries. For similar reasons it is difficult to state exactly what must be the duration of the circulatory arrest to produce syncope or convulsions.

In established complete heart block or in partial heart block the Stokes-Adams attack may belong to any group, whereas in paroxysmal heart block it is generally in Group I, i.e., ventricular standstill alone. After coronary thrombosis, attacks due to ventricular standstill alone may occur, as well as those due to ventricular tachycardia and fibrillation.

No prognostic significance can be attached to the grade of heart block, partial or complete, obtaining between the attacks, but the electrocardiographic nature of the attack has great significance in prognosis—and doubtless in treatment, although this is not considered here. Patients with ventricular standstill (Group I) have a fair chance of recovery and often survive for many years, whereas those with ventricular tachycardia and fibrillation (Groups II and III) seldom recover and then rarely survive for more than a year.

LeRoy, G. V., and Snider, S. S.: The Sudden Death of Patients With Few Symptoms of Heart Disease. *J. A. M. A.* 117: 2019, 1941.

The myocardial infarct responsible for sudden death need not be so large that muscular failure alone is responsible.

Myocardial infarction may occur without complete closure of a coronary artery and without the classic syndrome of pain, shock, and collapse.

A myocardial infarct usually causes some symptoms, even though they may be mild.

The sudden death of a patient with infarction of the myocardium is due to a reflex coronary vasoconstriction whose stimulus is the infarct, whose afferent pathway is the cardiosensory innervation, and whose efferent pathway is the vagus. The result of this reflex vasoconstriction in a susceptible person is fatal ventricular fibrillation.

The probability of the establishment of this lethal reflex may be decreased by the use of certain drugs (atropine and the xanthine derivatives), by cardiosensory denervation, and reasonably, but to a lesser extent, by simple rest in bed.

AUTHORS.

Cooke, W. T., and White, P. D.: Tricuspid Stenosis, With Particular Reference to Diagnosis and Prognosis. *Brit. Heart J.* 3: 147, 1941.

Between 1920 and 1937, 217 cases of rheumatic heart disease were observed in 4,300 autopsies at the Massachusetts General Hospital. In forty-seven of these, the tricuspid valve was affected, but in only thirty was tricuspid stenosis believed to be of sufficient degree to be of clinical significance.

In addition, twelve cases of tricuspid valve stenosis have been examined clinically by the authors during the past three years, including three cases that came to autopsy.

There were twenty-one males and twenty-one females in the combined groups of thirty-three autopsied and nine clinical cases.

The age at death varied between 10 and 59 years in the thirty cases with autopsies, and the average was 23 years. The average age at death in 160 cases of rheumatic heart disease in the same hospital was 42 years.

The cases of tricuspid valve disease may be divided into two groups: a young group in the first three decades dying of rheumatic fever, and an older group in whom the mechanical factors induced by the lesions played an increasingly important part.

The symptoms in the younger group were almost indistinguishable from those of rheumatic fever. The older group was characterized by the relatively long survival after the appearance of congestive symptoms and signs indicative, in most other circulatory disorders, of death in the near future.

The diagnosis of tricuspid disease in the young group indicates serious involvement of the myocardium and a poor prognosis. In the older group, owing to the "safety valve" function of the tricuspid valve, the patients may live many years providing there is no recurrence of severe rheumatic fever.

The diagnosis of tricuspid disease is difficult, but, when due attention is paid to the history, clinical examination of the patient, and x-ray examination of the heart, the diagnosis should be made more frequently. No one sign is pathognomonic, but in the order of importance the clues may be listed as follows (their chief value lies in combination): a mid-diastolic murmur localized over the tricuspid area, chronic and well-marked systolic pulsation of the deep jugular veins, ascites in the absence of lung congestion, enlargement of the heart shadow to the right, deviation of

the esophagus to the left, cyanosis and sometimes jaundice, enlarged liver with or without pulsation, persistently raised venous pressure, and prolonged right heart circulation time. The chief reason that the diagnosis is not made more often is that the physician does not look for these clues and signs.

The diagnosis of tricuspid disease is important as an aid in the more accurate determination of prognosis and treatment.

AUTHORS.

**Martin, A. T.: Twenty Years' Observation of 1,438 Children With Rheumatic Heart Disease. J. A. M. A. 117: 1663, 1941.**

A true evaluation of the results of convalescent care for children with rheumatic heart disease is not possible without a comparable control group of children kept in their home environment. Such a group of children was not available or possible for this study. The validity of any conclusions depends upon this.

Mortality figures were related closely to the severity of cardiac damage and were higher in the polycyclic types of rheumatic infection.

Future planning for children with rheumatic heart disease should provide prolonged bed rest and medical supervision, preferably in a sanatorium or foster home. This should follow care in the hospital. More beds should be provided for this purpose.

Convalescent care should be provided for a carefully selected group of children after the rheumatic infection has become quiescent and should be carried on for at least six months. Optimum benefit has been observed in the monocyclic group with minimal cardiac injury.

In the convalescent care of the cardiac child, attention to the psyche is quite as important as attention to the soma. The two should be integrated. The educational program and occupational therapy are important adjuncts in the process of rehabilitation.

The role of the trained social worker and adequate nursing supervision are important in the home when the child returns from the convalescent home or sanatorium.

AUTHOR.

**Clawson, B. J.: Relation of the "Anitschkow Myocyte" to Rheumatic Inflammation. Arch. Path. 32: 760, 1941.**

The "Anitschkow myocyte," the myocardial reticuloocyte (Ehrlich and Lapan) or the cardiac histiocyte, is normally found in the heart and heart valves.

It responds in inflammation by an increase in cytoplasm and is often the chief cell to respond in rheumatic inflammation and in experimental inflammation in the heart.

It is not a characteristic cellular response in rheumatic inflammation, for it is not found in rheumatic subcutaneous nodules.

AUTHOR.

**Stowell, D. D., and Button, W. H., Jr.: Observations of the Prophylactic Use of Sulfanilamide on Rheumatic Patients. J. A. M. A. 117: 2164, 1941.**

Sulfanilamide can be a lethal drug when used prophylactically on the rheumatic patient.

At the present state of knowledge the drug should not be used in ambulatory rheumatic children and adolescents.

AUTHORS.

Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subjects With Essential Hypertension. *J. Clin. Investigation* 20: 637, 1941.

The filtration rate ( $C_{in}$ ), diodrast clearance ( $C_d$ ) and the maximal rate of tubular excretion of diodrast ( $T_{md}$ ) have been examined in sixty subjects with essential hypertension. Comparison of the data with those previously reported for the normal kidney reveals the following facts.

An extreme reduction in  $T_{md}$  occurs in advanced states of the disease, and for the entire series of sixty subjects  $T_{md}$  is below or in the lower range; these facts lead us to infer that the disease is characterized by a progressive impairment of tubular function which proceeds at varying pace in different subjects.

In some patients impairment of tubular function appears to outrun impairment of glomerular function (formation of impotent tubules), so that the filtration rate remains within the limits of normal variation when  $T_{md}$  has been substantially reduced. In the nature of the renal circulation, elevation of the mean systemic blood pressure or the formation of impotent tubules may increase the quantity of diodrast-containing blood perfusing the residual functional tissue. We believe that in either case the anomalous condition will be revealed by the presence of a high filtration rate per unit of functional tubular tissue.

Deleting such anomalous instances, the effective blood flow per unit of functional tubular tissue, or the ratio  $C_d/T_{md}$ , in the remaining subjects, ranges downward from the mean normal to highly subnormal values, indicating relative renal ischemia. Since this ischemia is associated with an elevation of the filtration fraction, it is attributed to increased tone of the efferent glomerular arterioles. On the available evidence, this increased efferent tone may in turn be attributed to the presence of one or more pressor substances in the blood. The increased efferent tone is functionally reversible, in that renal hyperemia, associated with a fall in filtration fraction (efferent dilatation), follows the administration of suitable doses of pyrogen, as in normal subjects. The absolute values of  $C_d/T_{md}$  in hypertensive subjects during hyperemia are of the same order of magnitude as in normals during the hyperemic reaction.

In most hypertensive subjects,  $T_{md}$  has been reasonably constant over a considerable period and has not increased during pyrogenic hyperemia. In some subjects, however,  $T_{md}$  was increased during hyperemia, indicating that in these and perhaps in other subjects substantial quantities of tubular tissue may be ischemic under basal conditions. Spontaneous changes in  $T_{md}$  have been observed which may reflect changes in the quantity of tubular tissue available to perfusion or trophic changes in the excretory tissue itself.

In brief, the functional picture presented by the hypertensive kidney is consonant with the theory that there is present in the blood in hypertensive disease one or more pressor substances which produce a reversible renal ischemia by constriction of the efferent glomerular arterioles. In addition, there is profound impairment and ultimate destruction of tubular function. Which of these precedes the other is as yet undetermined.

There is no evidence in the present investigation to warrant the conclusion that renal ischemia is the primary cause of essential hypertension. The renal ischemia demonstrated here, which has its origin in increased tone of the efferent glomerular arterioles, appears to be one of the sequelae of the hypertensive process. We may place on record our belief that primary renal ischemia in man can, under proper quantitative circumstances, initiate a hypertensive process, but whether or not the secondary ischemia, associated with efferent hypertonus, which is present in hypertensive subjects generally, contributes to the progress of the disease cannot be

answered from this study. Alternatively, the possibility cannot yet be excluded that the appearance of pressor and cytotoxic substances in the blood follows a metabolic disorder in the kidney or in other organs and is wholly independent of renal ischemia.

AUTHORS.

**Chasis, H., and Redish, J.:** Effective Renal Blood Flow in the Separate Kidneys of Subjects With Essential Hypertension. *J. Clin. Investigation* 20: 655, 1941.

The clearance method has been applied to the measurement of the renal blood flow, the filtration rate, and the tubular excretory mass in the separate kidneys of patients with essential hypertension. The results of these observations indicate that the destruction of tubular tissue progresses equally on the two sides in hypertensive disease and that the functional disturbance in respect to blood flow and filtration rate is shared equally by the two kidneys.

In no instance in the twenty-one hypertensive subjects picked at random is there any indication of a unilateral ischemic kidney. If it is predicated that renal ischemia is the primary causal factor in all essential hypertension, it would be expected that unilateral impairment of renal function would be observed more frequently than bilateral impairment. The absence of unilateral impairment in these subjects argues against the above premise.

AUTHORS.

**Page, I. H.:** The Pressor Response of Normal and Hypertensive Dogs to Renin and Angiotonin. *Am. J. Physiol.* 134: 789, 1941.

Inconclusive evidence suggests that the blood vessels of hypertensive animals and man are abnormally sensitive to pressor agents; hence no more than normal amounts of them in the blood would be required to cause hypertension. It is, therefore, of importance to learn whether this is true of such substances as renin and angiotonin because of the belief that they may be involved in the genesis of chronic arterial hypertension. It is this problem with which this investigation is concerned.

Induction of experimental renal hypertension in dogs does not increase the pressor response to angiotonin. On the other hand, in such animals renin causes somewhat greater responses. The increased response to renin appears to be due to greater formation of angiotonin from combination of renin and renin-activator and is not the result of increased sensitivity of the vascular system of hypertensive animals.

AUTHOR.

**Coffen, T. H., Rush, H. P., and Miller, R. F.:** Traumatic Complete Heart Block of Eighteen Years' Duration. *Northwest Med.* 40: 195, 1941.

In this case it is believed that injury from a fall was followed by a lesion in the conducting pathway, resulting in auriculoventricular dissociation found seven years later when the patient was 10 years old. There have been no changes in the electrocardiograms in the last ten years. He has grown and developed normally and is following normal physical activities.

This case is reported because it is the only one in which auriculoventricular block from injury occurred in childhood that we have been able to find. There are only five other cases in which auriculoventricular block resulted from nonpenetrating injury. It has persisted for eighteen years in our patient. There have been no evidences of heart failure or Stokes-Adams syndrome.

AUTHORS.

Atlas, Lawrence N.: Traumatic Vasospastic Dystrophy of the Extremities. Arch. Surg. 42: 1042, 1941.

Trauma to an extremity with injury to a blood vessel or its nerve supply may result in a syndrome which the author calls traumatic vasospastic dystrophy. As a result of trauma to a blood vessel, without ischemia, there may occur pain, subjective and objective coldness, hyperhidrosis, cyanosis, tense, shiny skin, firm, tender edema, muscular weakness, joint fixation, and decalcification of bone. Three patients with this syndrome are presented. Theories as to the cause of the clinical picture are discussed.

NAIDE.

Roome, N. W.: Sympathetic Blockade in Peripheral Vascular Accidents. Canad. M. A. J. 44: 594, 1941.

Blockade of the lumbar sympathetic chain, by infiltration with procain solution, was found to give prompt and complete relief of otherwise intractable pain in two cases of embolism of the lower extremities.

The method is recommended for trial in cases of embolism, either alone or in combination with embolectomy, and should also be considered in the management of wounds of the major arteries, and of arterial thrombosis and acute thrombophlebitis.

AUTHOR.

Master, A. M.: Roentgenoscopy as a Diagnostic Aid in Coronary Occlusion. Am. J. Roentgenol. 45: 350, 1941.

Roentgenoscopic observations of ventricular contraction in 300 private patients are recorded. More than half of these had coronary occlusion; the remainder included other types of heart disease and normal subjects.

The technique employed is described in detail. Roentgenoscopy is shown to be a simple and inexpensive method of diagnosing coronary occlusion with myocardial infarction.

Abnormalities in pulsation were present in 75 per cent of the cases of coronary occlusion. Systolic expansion (reversal of pulsation) of the left ventricle, observed in 50 per cent of these cases, is characteristic, if not pathognomonic, of myocardial infarction. "Lag" and "doubling" of pulsation are incomplete forms of systolic expansion. Systolic expansion is seen in practically every case of large heart with ventricular aneurysm. Absence and diminution of pulsation were present in 25 per cent of cases with coronary occlusion, but also occurred in other types of heart disease.

The abnormal pulsations observed were located in the apical and the supra-apical portions of the left ventricle in almost 85 per cent of the cases studied.

The evidence of abnormal contraction did not depend upon the location of the infarct as determined electrocardiographically.

The incidence of abnormal pulsation in coronary occlusion was found to be greater when the heart was enlarged. When the area of abnormal pulsation was large, the prognosis was poor.

Systolic expansion may appear directly after the coronary occlusion and persist for many years. Its disappearance, or a change to absence or diminution of pulsation, is of favorable significance.

In normal hearts the pulsations are always normal. Hypertension alone does not produce changes. Disease of the coronary artery, without occlusion, did not exhibit systolic expansion or absence of pulsation. When these conditions are

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present, coronary occlusion should be suspected. Systolic expansion is seen occasionally in cases of aortic insufficiency with cardiac enlargement.

Roentgenoscopy should form part of the routine examination of every cardiac suspect. It may be positive when the physical examination and electrocardiogram are negative.

AUTHOR.

Sheehan, D., Mulholland, J. H., and Shafiroff, B.: Surgical Anatomy of the Carotid Sinus Nerve. *Anat. Rec.* 80: 431, 1941.

The common variations of the carotid sinus nerve and of the innervation of the carotid body have been described, based on thirty-three special dissections of this region.

The carotid sinus is innervated by the glossopharyngeal, vagus and cervical sympathetic, and exceptionally by the hypoglossal. The fibers reach the sinus in two ways, (1) along the carotid sinus nerve and (2) through an intercarotid plexus and the carotid body.

The anatomy suggests the feasibility of dividing the carotid sinus nerve in preference to extensive stripping of the carotid artery, in the surgical treatment of carotid sinus syncope.

AUTHORS.

Hyman, A., and Leiter, H. E.: Surgery of the Inferior Vena Cava in Urologic Conditions. *J. Urol.* 45: 813, 1941.

A series of eleven surgical procedures on the vena cava is reported. Experimental and surgical procedures demonstrate that complete ligation of the cava below the renal veins is compatible with life. In this series the vena cava was accidentally injured in four instances, whereas in the other seven cases the surgery was deliberate. It may be stated that the deliberate type of surgery on the cava is generally associated with renal neoplasms or adherent pyonephrotic kidneys. With the newer sulfanilamide preparations in general use, the indications for surgery on the cava in inflammatory conditions will be reduced to a minimum. In these eleven cases there were three postoperative deaths. As stressed in this paper, the renal vein and vena cava should always be explored in right renal neoplasms. For this reason, a wide exposure, necessitating resection of one or two ribs, is advisable. In some of the cases reported patients have survived a three-year period where thrombi have been removed from the vena cava. The presence of a vena cava tumor thrombus, while certainly grave, does not necessarily imply an immediate fatal course.

AUTHORS.

Pratt, G. H., and Wright I. S.: The Surgical Treatment of Chronic Lymphedema (Elephantiasis). *Surg., Gynec. & Obst.* 72: 244, 1941.

A surgical procedure is described for the treatment of chronic lymphedema. The importance of proper preoperative preparation is stressed. About three-fourths of the circumference of the superficial and deep fascia are excised en masse. A broad-based pedicle tube graft is employed where it is necessary to remove devitalized skin. In addition to skin replacement, the pedicled graft drains the skin lymphatics and thus supplies a new method of aiding skin lymphatic drainage.

NAIDE.

Friedbacher, K.: *Experimental Collateral Circulation of the Heart.* Surg., Gynec. & Obst. 72: 1003, 1941.

The author's experiments tend to show the following conclusions.

The direct anastomosis of internal mammary artery to the coronary might be possible.

The omental graft lends itself best as a possible source of extracardiac blood supply to the myocardium. The graft remains pliable, and the heart action is free.

Muscle grafts become quite firm and interfere with heart action; a layer of fibrosis develops between skeletal and myocardial muscles.

The heart of the healthy dog withstands diminution of its normal blood supply until it reaches the point of infarction and then recovers as demonstrated by the electrocardiogram.

Vascular connections between the graft and the heart muscle can be demonstrated in microscopic dissections.

Additional experiments are being carried out at the present time to prove further these contentions.

AUTHOR.

Cole, W. H., Weber, R. D., and Keeton, R. W.: *Pericardiectomy for Chronic Constrictive Pericarditis.* Surg., Gynec. & Obst. 72: 1008, 1941.

Undoubtedly, innumerable cases of constrictive pericarditis are erroneously diagnosed as congestive heart failure, hepatic cirrhosis, etc., because of the similarity of symptoms to those of constrictive pericarditis. It is particularly important that this error be avoided because sufficient operative reports are now available to establish the fact that, although the mortality rate is high, the results otherwise are excellent. Perhaps the first symptom of constrictive pericarditis is weakness, followed soon by dyspnea upon exertion. Of great diagnostic significance is the fact that in this disease the dyspnea is not present while the patient is inactive and that ascites precedes edema of the extremities. Distended neck veins, high venous pressure, paradoxical pulse, and small cardiac shadow constitute important evidence for the diagnosis.

Since conservative treatment of the disease is hopeless, operation should be performed early, before myocardial damage due to compression, etc., is irreparable. Results are much better in young people; very few patients in adult life survive the operation. Results may not be immediate, as emphasized by the fact that in one of our patients strength was still subnormal one year following operation, but two years after operation he felt perfectly normal and was working daily running a press.

AUTHORS.

Bigger, I. A.: *Peripheral Vascular Injuries.* Ann. Surg. 113: 677, 1941.

The treatment of injuries to the major peripheral vessels forms an important part of modern war surgery. In the past, even during the World War I, vascular suture was not often feasible. Since we now have more effective means of preventing thrombosis at the line of suture, and of combating infection, suture should play a more important role in reducing peripheral gangrene due to vascular injuries.

When important arteries are occluded, certain measures should be employed to combat ischemia, among them ligation of the concomitant vein or veins and, if there



is any evidence of insufficient collateral circulation, sympathetic nerve block. In addition to these local measures, certain general measures, of which the most important is blood replacement, must also be given consideration.

NAIDE.

**Homans, John:** Minor Causalgia Following Injuries and Wounds. *Ann. Surg.* 113: 932, 1941.

The author discusses a symptom complex of pain in the extremities following trauma involving nerves and blood vessels. Causalgia arises from a variety of injuries, including blows, crushes, fractures, puncture wounds, and animal bites. The mechanism by which the pain is produced is not definitely known but is thought to be the result of irritation of nerves in blood vessel walls, the vessels themselves often supplying nerve trunks. At any rate, it has been shown that the pain can be abolished by cutting off sympathetic impulses from the affected part. This can be done by sympathetic block by procaine.

NAIDE.

**Bradley, S. E., and Parker, B.:** The Hemodynamic Effects of Angiotonin in Normal Man. *J. Clin. Investigation* 20: 715, 1941.

Cardiac output, mean arterial pressure, peripheral resistance, and efficient elasticity modulus have been determined following intravenous administration of angiotonin.

In all experiments, mean arterial pressure and peripheral resistance rose sharply. The pulse pressure tended to widen. With one exception, the efficient elasticity modulus rose sharply. Cardiac output fell as a result of a marked bradycardia. There was little change in stroke volume and, where a change occurred, it was in the direction of a decrease. Response to small single injections and to continuous intravenous infusions differed only in the absence of bradycardia in the latter.

Kymorontgenogram and cardiocairogram studies revealed little change in heart size. However, there was present a consistent decrease in amplitude of ventricular waves.

It is concluded that angiotonin acts directly upon the musculature of the cardiovascular system, producing arteriolar vasoconstriction and possibly increased "cardia tone." Whether the distensibility of the central arterial reservoir is specifically decreased by angiotonin, or whether the observed change is attributable simply to increased distention of the central arteries, cannot be answered with certainty from the present data.

AUTHORS.

**Wilkins, R. W., and Duncan, C. N.:** The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin. *J. Clin. Investigation* 20: 721, 1941.

Angiotonin administered intravenously in normal subjects produces arterial hypertension which can be controlled by regulating the rate of administration.

This arterial hypertension is accompanied by an increase of venous pressure and frequently by other signs of "myocardial failure," including (a) decrease in vital capacity, (b) increase in circulation time, (c) decrease in cardiac output, and (d) increase in cardiac size. There is bradycardia, probably vagal in origin. Spinal fluid pressure is not significantly altered. The electrocardiogram reveals no important changes except bradycardia. The temperature of the skin usually decreases but remains responsive to alterations of body temperature. Blood flow measured plethysmographically in the limbs tends to decrease but remains

under the control of the sympathetic nervous system. Reactive-hyperemia blood flow (measured during full local vasodilatation produced by a five-minute period of arterial occlusion) increases with the rise of arterial pressure. The pressor response to the cold test of Hines and Brown is not altered during the hypertension. Mild symptoms of dizziness, substernal oppression, headache, nausea, or palpitation may be noted. The effects subside four to ten minutes after the cessation of administration, whether by single injection or by continuous infusion. Injected intradermally, angiotonin produces local blanching of the skin. Injected intra-arterially, it produces vasoconstriction in the muscular parts supplied by the artery.

AUTHORS.

**Kirk, R. C., and Kilpatrick, E. M.: Ventricular Paroxysmal Tachycardia From Adrenalin and Sinus Standstill From Intravenous Quinidine in a Case of Coronary Occlusion. Ohio State M. J. 37: 437, 1941.**

A case of coronary occlusion is presented which developed ventricular tachycardia following the use of adrenalin chloride in a digitalized heart. Efforts to restore normal rhythm by intravenous quinidine were followed by sinus arrest and sudden death. An autopsy disclosed an old anterior coronary occlusion with a recent posterior coronary occlusion complicated by a large mesenteric infarction.

AUTHORS.

**Bonnell, R. W., Pritchett, C. P., and Hardin, T. E.: Treatment of Angina Pectoris and Coronary Artery Disease With Sex Hormones. Ohio State M. J. 37: 554, 1941.**

Twenty-three patients with coronary artery disease, twenty-one of them having angina pectoris, were treated with sex hormones. Clinical improvement was noted in twenty-two of the twenty-three patients. Both estrogens and androgens were used.

Experimental evidence is cited which indicates that the sex hormones have a vasodilating property. It is thought that the improvement in this series of patients is due to a vasodilating property of the sex hormones acting on the coronary circulation.

AUTHORS.

**Evans, G.: The Effect of Insulin on Cardiac and Liver Glycogen. Am. J. Physiol. 134: 798, 1941.**

Rats were injected intravenously with glucose with or without insulin. Cardiac glycogen was found to be increased by glucose, but not further increased by the addition of insulin.

In the animals injected with glucose, the liver glycogen was found to be lowered by insulin and progressively so as the dose was increased; the effect occurs even during hyperglycemia; it is not mediated by the adrenal. Possible explanations are discussed.

AUTHOR.

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*\*Executive Committee.*

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## Original Communications

### FURTHER STUDIES IN IMMUNIZATION AGAINST RHEUMATIC FEVER

VALENTINA P. WASSON, M.D., AND EDWARD E. BROWN, M.D.  
NEW YORK, N. Y.

IN JULY, 1940, we<sup>1</sup> reported the results of immunization against recurrences of acute rheumatic fever in thirty-one children who were known to have rheumatic heart disease, or to be potential cardiac patients. A follow-up study of thirty-five other patients who had received the same treatment elsewhere was included.

In September, 1939, we began to immunize a new group of forty-three cardiac children by the same method, and in September, 1940, we added another group of forty-two rheumatic cardiac patients who have been given a modified form of treatment. This paper includes a survey of these two groups and of a control group and also a follow-up study of sixty-six previously treated patients, with their corresponding control groups.

The treatment that forty-three children began to receive in September, 1939, and that lasted for two consecutive winters, consisted of repeated injections of graduated doses of hemolytic streptococcus filtrate (N. Y. 5 strain). The preparation of the filtrate and the procedure of immunization were given in detail by us<sup>2</sup> in 1939. Here we shall report only on the present progress of treatment.

For the sake of clarity the data obtained from the group of patients who began treatment in 1939 will be discussed in two stages, namely, the results of the first winter, and the results of the second winter, in each case in comparison with the respective control group. The distinction between the two years is necessary because the control patients were not the same in both years. The same observation applies to

This work was carried out at the New York Post-Graduate Hospital and Medical School under the auspices of the Department of Pediatrics, and it was financed by the John and Mary R. Markle Foundation.

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formerly treated patients who have been followed carefully in the clinic and whose health has to be compared with that of patients who have never had any specific treatment.

The original group of patients in the fall of 1939 consisted of forty-three rheumatic cardiac and potential cardiac children, of whom sixteen were males, and twenty-seven, females. Their mean age was 11.6 years (Table I). The average number of reported colds per child was 3.6 for the first winter, and the average gain in weight, 5.7 pounds. Among subacute rheumatic complaints, abdominal symptoms were reported frequently by six patients; chronic pallor, by nine; epistaxis on more than two occasions, by three; joint and muscle pains, by six; cardiac symptoms, such as dyspnea and precordial pain, by five; headaches, by eighteen; and twitching, by five. There were three attacks of acute rheumatic fever. To aid in diagnosis we used the erythrocyte sedimentation rate, the hemoglobin estimation, and the Schilling and platelet counts on all patients. The laboratory procedure which we employed was described by us recently.<sup>3</sup>

In 1939 to 1940 the mean laboratory values for the treated group were: erythrocyte sedimentation rate, 9.6 mm. per hour;\* hemoglobin, 72.2 per cent; nonfilamented cell count, 11.4 per cent; and platelet count, 179,000 per cubic millimeter.

In the past, under "Results," we gave our opinion of the patient's rheumatic state at the end of each year. In this paper we give our opinion of the patient's condition at the beginning of each year, e.g., September, and at the end, e.g., late June. These opinions are based on careful clinical and laboratory data for each patient.†

The control group for the same year comprised forty-five patients, of whom twenty-nine were males, and sixteen, females. The average age was approximately the same as in the treated group. The control group showed fewer colds and more gain in weight than the treated group. The subacute rheumatic symptoms were much more troublesome in the untreated group, and there were nineteen attacks of rheumatic fever, chorea, and carditis, together with one death. Twelve of the nineteen were hospitalized.

In September, 1940, only thirty-five children started the second year of treatment, for four had moved away, two had decided that they were too well to continue the injections, one could not be traced, and one was transferred to a group which was receiving a modified form of treatment, to be described below.

The group of thirty-five who continued treatment was made up of twelve boys and twenty-three girls whose average age was 11.7 years

\*Linzenmeyer-Rounert microsedimentation method was used.

†We have not used the therapeutic classification established by the New York Heart Association because it was introduced during the course of our observations, and, at least initially, the application of the new classification was not uniform among the physicians at the clinics.

TABLE I  
COMPARISON BETWEEN TREATED AND CONTROL PATIENTS DURING 1939-1940

|   | TREATED               |                         | CONTROL               |                         |
|---|-----------------------|-------------------------|-----------------------|-------------------------|
| No. of patients   | 43                    |                         | 45                    |                         |
| Sex   | 16 males; 27 females  |                         | 29 males; 16 females  |                         |
| Av. age (yr.)   | 11.6                  |                         | 11.5                  |                         |
| No. of reported colds per child                         | 3.6                   |                         | 2.3                   |                         |
| Mean weight gain (lb.)                                  | 5.7                   |                         | 7.5                   |                         |
| Abdominal symptoms                                      |                       |                         |                       |                         |
| +   | 13                    |                         | 9                     |                         |
| ++  | 1                     |                         | 3                     |                         |
| +++   | 6                     |                         | 6                     |                         |
| Pallor  |                       |                         |                       |                         |
| +   | 6                     |                         | 5                     |                         |
| ++  | 2                     |                         | 7                     |                         |
| +++   | 9                     |                         | 11                    |                         |
| Epistaxis   |                       |                         |                       |                         |
| +   | 8                     |                         | 2                     |                         |
| ++  | 1                     |                         | 4                     |                         |
| +++   | 3                     |                         | 3                     |                         |
| Rheumatic pains   |                       |                         |                       |                         |
| +   | 5                     |                         | 7                     |                         |
| ++  | 11                    |                         | 7                     |                         |
| +++   | 6                     |                         | 12                    |                         |
| Cardiac symptoms  |                       |                         |                       |                         |
| +   | 7                     |                         | 6                     |                         |
| ++  | 3                     |                         | 8                     |                         |
| +++   | 5                     |                         | 6                     |                         |
| Headaches   |                       |                         |                       |                         |
| +   | 3                     |                         | 4                     |                         |
| ++  | 3                     |                         | 7                     |                         |
| +++   | 18                    |                         | 11                    |                         |
| Twitching   |                       |                         |                       |                         |
| +   | 4                     |                         | 3                     |                         |
| ++  | 3                     |                         | 1                     |                         |
| +++   | 5                     |                         | 7                     |                         |
| No. of attacks of rheumatic fever, carditis, and chorea | 3, or 7%              |                         | 19, or 40.2%          |                         |
| Deaths  | 0                     |                         | 1                     |                         |
| Mean laboratory data:                                   |                       |                         |                       |                         |
| E.S.R. (mm. per hr.)                                    | 9.6                   |                         | 12.5                  |                         |
| Hemoglobin (%)  | 72.2                  |                         | 73.4                  |                         |
| Nonfilamented neutrophils (%)                           | 11.4                  |                         | 9.3                   |                         |
| Platelets (per cu. mm.)                                 | 179,000               |                         | 186,000               |                         |
| Estimation of patient's condition:                      |                       |                         |                       |                         |
|   | <i>Fall</i><br>(1939) | <i>Spring</i><br>(1940) | <i>Fall</i><br>(1939) | <i>Spring</i><br>(1940) |
| Excellent   | 5                     | 10                      | 14                    | 12                      |
| Very good   | 5                     | 11                      | 9                     | 7                       |
| Good  | 9                     | 9                       | 4                     | 3                       |
| Av.   | 11                    | 8                       | 6                     | 3                       |
| Fair  | 10                    | 2                       | 5                     | 1                       |
| Poor  | 3                     | 3                       | 7                     | 19                      |

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

TABLE II  
COMPARISON BETWEEN TREATED AND CONTROL PATIENTS DURING 1940-1941

|   | TREATED                      |                                | CONTROL                      |                                |
|---|------------------------------|--------------------------------|------------------------------|--------------------------------|
| No. of patients   | 35                           |                                | 33                           |                                |
| Sex   | 12 males; 23 females         |                                | 17 males; 16 females         |                                |
| Av. age (yr.)   | 11.7                         |                                | 12.1                         |                                |
| No. of reported colds per child                         | 3                            |                                | 2.9                          |                                |
| Mean weight gain (lb.)                                  | 9.2                          |                                | 7.9                          |                                |
| Abdominal symptoms                                      |                              |                                |                              |                                |
| +   | 9                            |                                | 4                            |                                |
| ++  | 2                            |                                | 4                            |                                |
| +++   | 3                            |                                | 5                            |                                |
| Pallor  |                              |                                |                              |                                |
| +   | 9                            |                                | 3                            |                                |
| ++  | 1                            |                                | 1                            |                                |
| +++   | 4                            |                                | 12                           |                                |
| Epistaxis   |                              |                                |                              |                                |
| +   | 4                            |                                | 3                            |                                |
| ++  | 4                            |                                | 4                            |                                |
| +++   | 1                            |                                | 0                            |                                |
| Rheumatic pains   |                              |                                |                              |                                |
| +   | 8                            |                                | 3                            |                                |
| ++  | 2                            |                                | 3                            |                                |
| +++   | 4                            |                                | 14                           |                                |
| Cardiac symptoms  |                              |                                |                              |                                |
| +   | 4                            |                                | 5                            |                                |
| ++  | 2                            |                                | 1                            |                                |
| +++   | 3                            |                                | 10                           |                                |
| Headaches   |                              |                                |                              |                                |
| +   | 7                            |                                | 1                            |                                |
| ++  | 2                            |                                | 1                            |                                |
| +++   | 6                            |                                | 11                           |                                |
| Twitching   |                              |                                |                              |                                |
| +   | 1                            |                                | 2                            |                                |
| ++  | 2                            |                                | 2                            |                                |
| +++   | 2                            |                                | 4                            |                                |
| No. of attacks of rheumatic fever, carditis, and chorea | 4, or 11.4%                  |                                | 11, or 33%                   |                                |
| Deaths  | 0                            |                                | 3                            |                                |
| Mean laboratory data:                                   |                              |                                |                              |                                |
| E.S.R. (mm. per hr.)                                    | 9.4                          |                                | 17                           |                                |
| Hemoglobin (%)  | 74.3                         |                                | 73.2                         |                                |
| Nonfilamented neutrophils (%)                           | 8                            |                                | 10.5                         |                                |
| Platelets per cu. mm.                                   | 200,000                      |                                | 192,000                      |                                |
| Estimation of the patient's condition:                  | <i>Fall</i><br><i>(1940)</i> | <i>Spring</i><br><i>(1941)</i> | <i>Fall</i><br><i>(1940)</i> | <i>Spring</i><br><i>(1941)</i> |
| Excellent   | 9                            | 14                             | 10                           | 8                              |
| Very good   | 11                           | 10                             | 4                            | 2                              |
| Good  | 8                            | 3                              | 5                            | 4                              |
| Av.   | 7                            | 2                              | 5                            | 4                              |
| Fair  | 1                            | 2                              | 5                            | 4                              |
| Poor  | 0                            | 4                              | 4                            | 11                             |

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

(Table II). The average number of upper respiratory infections was three for twelve months (June, 1940, to June, 1941), and the mean gain in weight for the same period was 9.2 pounds per child. The subacute rheumatic symptoms abated markedly during the second winter of treatment; considerably fewer patients showed pallor, abdominal symptoms, epistaxis, and joint and muscle pains. Chronic headaches, which were present in eighteen patients during the first winter of treatment, were troublesome only in six children. Four patients, or 11.4 per cent, suffered one attack each of acute rheumatic fever. The laboratory data showed little change from the preceding year. However, the nonfilamented neutrophile count dropped to normal, and the platelet count showed a moderate increase.

The control group during the second year of treatment consisted of thirty-three patients. Twenty of these were carried over from the preceding year, and the rest were newcomers in September, 1940.

There were seventeen boys and sixteen girls in this group (Table II). Their average age was 12.1 years. The number of reported colds per child was 2.9, and the mean gain in weight, 7.9 pounds. The subacute rheumatic fever symptoms were many and severe, except for the absence of nosebleeds. There were eleven attacks of rheumatic fever, with three deaths.

*Formerly Treated Group.*—In order to estimate the more remote effects of this form of immunization against rheumatic fever, the group of patients who were treated from 1937 to 1939 was carefully followed in the cardiac research clinic. They received the same attention as the control patients. It is only natural that, with the passing of time, this group has dwindled somewhat. Of thirty-one patients, six failed to return for follow-up study after they had been told that they had received their last "needle." Four patients who had attended the clinic regularly also vanished. Therefore, twenty-five of thirty-one formerly treated patients have been observed regularly during 1939 to 1940, and twenty-one of those, during 1940 to 1941. The regularity of their attendance was excellent.

The condition of the twenty-five formerly treated patients who attended the clinic during 1939 to 1940 is compared with that of the already discussed control group of forty-five patients for that year, and the twenty-one formerly treated patients who were observed during 1940 to 1941 are compared with the control group of thirty-three children.

Naturally, the formerly treated patients are considerably older than those with whom they are being compared from year to year. The clinic is not large enough to carry separate control groups for formerly and presently treated patients. The control group varies from year to year partly because untreated patients are less well disciplined with respect to regular attendance, partly because many ask to be immunized and



join the new groups who are getting treatment, and partly because we are trying now to make them similar in age and severity of heart disease with the groups that receive active treatment. In the latter a few patients may drop out in the course of treatment, but after the first months no new ones are taken. Thus the treated groups remain constant in composition, and the control group is constant in age.

*The Follow-up Study of Formerly Treated Patients.*—In 1939 to 1940 the mean age of the twenty-five formerly treated patients was 14.8 years (Table III). The mean gain in weight for the twelve months was 7.25 pounds, and the average number of reported upper respiratory infections was two. Among frequent subacute symptoms, abdominal distress occurred in two patients; bodily pains, in three; dyspnea and precordial pain, in one; and headaches in four. There were three attacks (12 per cent) of acute rheumatic fever. The average hematologic observations were all within normal limits.

The average age of forty-five control patients for the same period was 11.5 years. Their average gain in weight and the number of reported colds were approximately the same as in the group just mentioned. Among frequent subacute symptoms, abdominal pain and vomiting occurred in six; pallor in eleven; epistaxis in three; rheumatic pains in twelve; cardiac symptoms in six; headaches in eleven; and twitching in seven. There were nineteen instances (40.2 per cent) of acute rheumatic fever attacks, with one death. The mean sedimentation rate was 4.5 mm. per hour higher, and the nonfilamented neutrophile count 1.3 per cent higher.

During the winter of 1940 to 1941 the remaining twenty-one formerly treated patients fared even better (Table IV). The gain in weight for the year was 8.45 pounds. Only two complained of chronic abdominal symptoms; one showed chronic pallor; two had many nosebleeds, two had frequent joint and muscle pains; and two had chronic headaches. Only one patient (4.76 per cent) developed an attack of rheumatic fever. The average blood picture was normal.

A comparison with the control group of thirty-three patients in the same year shows that, although the gain in weight and the average number of colds were about the same, the subacute rheumatic fever symptoms in the control group were distressingly high; also, there were eleven acute rheumatic fever attacks, with three deaths.

In our effort to delve still further into the effects of immunization against rheumatic fever over a period of years, we have been fortunate in receiving permission\* to examine and question all available patients who were under study prior to 1937. We first reported on their condition in June, 1939.<sup>1</sup> The second "round-up" of this group took place in June, 1941.

\*Courtesy of Flower-Fifth Avenue Hospital.

TABLE III

COMPARISON BETWEEN FORMERLY TREATED AND CONTROL PATIENTS IN 1939-1940

|   | FORMERLY TREATED    | CONTROL              |
|---|---------------------|----------------------|
| No. of patients   | 25                  | 45                   |
| Sex   | 16 males; 9 females | 29 males; 16 females |
| Av. age (yr.)   | 14.8                | 11.5                 |
| No. of reported colds per child                         | 2                   | 2.3                  |
| Mean weight gain (lb.)                                  | 7.25                | 7.5                  |
| Abdominal symptoms                                      |                     |                      |
| +   | 7                   | 9                    |
| ++  | 0                   | 3                    |
| +++   | 2                   | 6                    |
| Pallor  |                     |                      |
| +   | 0                   | 5                    |
| ++  | 2                   | 7                    |
| +++   | 2                   | 11                   |
| Epistaxis   |                     |                      |
| +   | 2                   | 2                    |
| ++  | 1                   | 4                    |
| +++   | 0                   | 3                    |
| Rheumatic pains   |                     |                      |
| +   | 1                   | 7                    |
| ++  | 2                   | 7                    |
| +++   | 3                   | 12                   |
| Cardiac symptoms  |                     |                      |
| +   | 1                   | 6                    |
| ++  | 0                   | 8                    |
| +++   | 1                   | 6                    |
| Headaches   |                     |                      |
| +   | 2                   | 4                    |
| ++  | 1                   | 7                    |
| +++   | 4                   | 11                   |
| Twitching   |                     |                      |
| +   | 0                   | 3                    |
| ++  | 0                   | 1                    |
| +++   | 0                   | 7                    |
| No. of attacks of rheumatic fever, carditis, and chorea | 3, or 12%           | 19, or 40.2%         |
| Deaths  | 0                   | 1                    |
| Mean laboratory data:                                   |                     |                      |
| E.S.R. (mm. per hr.)                                    | 8                   | 12.5                 |
| Hemoglobin (%)  | 74                  | 73.4                 |
| Nonfilamented neutrophils (%)                           | 8                   | 9.3                  |
| Platelets per cu. mm.                                   | 185,000             | 186,000              |
| Estimation of patient's condition:                      |                     |                      |
|   | Fall (1939)         | Spring (1940)        |
| Excellent   | 12                  | 16                   |
| Very good   | 6                   | 4                    |
| Good  | 4                   | 0                    |
| Av.   | 1                   | 2                    |
| Fair  | 1                   | 0                    |
| Poor  | 1                   | 3                    |
|   |                     | Fall (1939)          |
|   |                     | Spring (1940)        |
|   |                     | 14                   |
|   |                     | 12                   |
|   |                     | 9                    |
|   |                     | 7                    |
|   |                     | 4                    |
|   |                     | 3                    |
|   |                     | 6                    |
|   |                     | 3                    |
|   |                     | 5                    |
|   |                     | 1                    |
|   |                     | 7                    |
|   |                     | 19                   |

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

TABLE IV

COMPARISON BETWEEN FORMERLY TREATED AND CONTROL PATIENTS IN 1940-1941

|   | FORMERLY TREATED    |               | CONTROL              |               |
|---|---------------------|---------------|----------------------|---------------|
| No. of patients   | 21                  |               | 33                   |               |
| Sex   | 13 males; 8 females |               | 17 males; 16 females |               |
| Av. age (yr.)   | 15.8                |               | 12.1                 |               |
| No. of reported colds per child                         | 2.2                 |               | 2.9                  |               |
| Mean weight gain (lb.)                                  | 8.45                |               | 7.9                  |               |
| Abdominal symptoms                                      |                     |               |                      |               |
| +   | 2                   |               | 4                    |               |
| ++  | 0                   |               | 4                    |               |
| +++   | 2                   |               | 5                    |               |
| Pallor  |                     |               |                      |               |
| +   | 1                   |               | 3                    |               |
| ++  | 1                   |               | 1                    |               |
| +++   | 1                   |               | 12                   |               |
| Epistaxis   |                     |               |                      |               |
| +   | 2                   |               | 3                    |               |
| ++  | 1                   |               | 4                    |               |
| +++   | 2                   |               | 0                    |               |
| Rheumatic pains   |                     |               |                      |               |
| +   | 5                   |               | 3                    |               |
| ++  | 0                   |               | 3                    |               |
| +++   | 2                   |               | 14                   |               |
| Cardiac symptoms  |                     |               |                      |               |
| +   | 2                   |               | 5                    |               |
| ++  | 0                   |               | 1                    |               |
| +++   | 0                   |               | 10                   |               |
| Headaches   |                     |               |                      |               |
| +   | 1                   |               | 1                    |               |
| ++  | 3                   |               | 1                    |               |
| +++   | 2                   |               | 11                   |               |
| Twitching   |                     |               |                      |               |
| +   | 1                   |               | 2                    |               |
| ++  | 0                   |               | 2                    |               |
| +++   | 0                   |               | 4                    |               |
| No. of attacks of rheumatic fever, carditis, and chorea | 1, or 4.76%         |               | 11, or 33%           |               |
| Deaths  | 0                   |               | 3                    |               |
| Mean laboratory data:                                   |                     |               |                      |               |
| E.S.R. (mm. per hr.)                                    | 9.6                 |               | 17                   |               |
| Hemoglobin (%)  | 77                  |               | 73.2                 |               |
| Nonfilamented neutrophils (%)                           | 7.4                 |               | 10.5                 |               |
| Platelets per cu. mm.                                   | 180,000             |               | 192,000              |               |
| Estimation of the patient's condition:                  | <i>Fall</i>         | <i>Spring</i> | <i>Fall</i>          | <i>Spring</i> |
|   | <i>(1940)</i>       | <i>(1941)</i> | <i>(1940)</i>        | <i>(1941)</i> |
| Excellent   | 12                  | 12            | 10                   | 8             |
| Very good   | 4                   | 6             | 4                    | 2             |
| Good  | 0                   | 1             | 5                    | 4             |
| Av.   | 2                   | 1             | 5                    | 4             |
| Fair  | 0                   | 0             | 5                    | 4             |
| Poor  | 3                   | 1             | 4                    | 11            |

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

TABLE V

COMPARISON BETWEEN FORMERLY TREATED AND CONTROL PATIENTS IN 1939-1941

|  | FORMERLY TREATED<br>(1933-35-37) |               | CONTROL            |               |
|--|----------------------------------|---------------|--------------------|---------------|
| No. patients                           | 22                               |               | 12                 |               |
| Sex                                    | 14 males; 9 females              |               | 6 males; 6 females |               |
| Av. age                                | 13.2                             |               | 15                 |               |
| No. of reported colds per child        | 1.6                              |               | 3                  |               |
| Av. gain in weight (lb.) (2 yr.)       | 23.5                             |               | 13.9               |               |
| Abdominal symptoms                     |                                  |               |                    |               |
| +                                      | 0                                |               | 1                  |               |
| ++                                     | 1                                |               | 2                  |               |
| +++                                    | 1                                |               | 1                  |               |
| Pallor                                 |                                  |               |                    |               |
| +                                      | 0                                |               | 0                  |               |
| ++                                     | 0                                |               | 0                  |               |
| +++                                    | 0                                |               | 1                  |               |
| Epistaxis                              |                                  |               |                    |               |
| +                                      | 0                                |               | 0                  |               |
| ++                                     | 2                                |               | 0                  |               |
| +++                                    | 0                                |               | 2                  |               |
| Joint pains                            |                                  |               |                    |               |
| +                                      | 5                                |               | 0                  |               |
| ++                                     | 1                                |               | 2                  |               |
| +++                                    | 1                                |               | 4                  |               |
| Cardiac symptoms                       |                                  |               |                    |               |
| +                                      | 1                                |               | 1                  |               |
| ++                                     | 0                                |               | 0                  |               |
| +++                                    | 1                                |               | 4                  |               |
| Headaches                              |                                  |               |                    |               |
| +                                      | 4                                |               | 0                  |               |
| ++                                     | 0                                |               | 2                  |               |
| +++                                    | 1                                |               | 3                  |               |
| Twitching                              |                                  |               |                    |               |
| +                                      | 0                                |               | 0                  |               |
| ++                                     | 0                                |               | 2                  |               |
| +++                                    | 0                                |               | 0                  |               |
| Attacks of rheumatic fever             | 1, possibly 2                    |               | 3                  |               |
| Estimation of the patient's condition: | <i>Spring</i>                    | <i>Spring</i> | <i>Spring</i>      | <i>Spring</i> |
|  | (1939)                           | (1941)        | (1939)             | (1941)        |
| Excellent                              | 12                               | 11            | 1                  | 1             |
| Very good                              | 5                                | 4             | 1                  | 1             |
| Good                                   | 2                                | 3             | 2                  | 3             |
| Av.                                    | 1                                | 2             | 2                  | 1             |
| Fair                                   | 0                                | 1             | 2                  | 3             |
| Poor                                   | 2                                | 1             | 4                  | 3             |

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

Of the original group of thirty-five treated patients, eighteen reappeared four years later for re-examination. Four did not come, although their recent cardiac clinic records were available, and thus they may be included here. The remaining thirteen have been dropped, either because of age or change of residence, and they could not be traced.

Hence we have the record of twenty-two patients, which is, needless to say, a brief one, for the only sources were the relatively infrequent entries in the cardiac charts (thanks to the children's good health), the memory of the patients and their relatives, and a physical examination by one of us. Blood cell counts and sedimentation rates were performed only when needed, and, since this group, with one exception, enjoyed excellent health, they are too few for statistical appraisal. The clinical record is as follows (Table V): In this group of formerly treated patients whose records are up to date there were nine girls and fourteen boys. Their mean age in June, 1941, was 13.2 years. The average gain in weight was 23.5 pounds per child over twenty-four months. The number of colds reported was 1.6 per patient for two years, which is probably too low because of forgetfulness, and the tendency of the older children, when unaccompanied by their parents, to lean toward optimism. Among the subacute symptoms which were remembered by them over a two-year period or were recorded in the New York Heart Association charts, the following occurred more than twice: abdominal pain and vomiting in one, joint and muscle pains in one, cardiac symptoms in one, and headaches in one. One attack of rheumatic fever and one attack of "abdominal grippe" which lasted for a week were recorded. But since the latter patient now shows not only mitral insufficiency and stenosis but also aortic insufficiency, it is safe to assume that he suffered an attack of acute rheumatism in which abdominal symptoms were prominent and joint pains absent.

The corresponding control group yielded information about twelve patients, eight of whom appeared for examination; the recent records of four others are available. Of this group, six were boys and six girls. Their average age at the time of their visit in June, 1941, was 15 years. The mean gain in weight per patient in twenty-four months was 13.9 pounds, or 7 pounds per year. There were three attacks of acute rheumatic fever (25 per cent) and one attack of scarlet fever. Almost all of the children were in a mediocre state of health and had a long list of complaints. They reported an average of three colds for the same period, which is not high, but almost double that of the treated group. Of the twelve, one complained of chronic abdominal pains; two, of frequent nosebleeds; four, of chronic joint and muscle pains; four, of cardiac symptoms; and three, of chronic headaches. Only one said unequivocally that she had no complaints, whereas in the group of formerly treated patients eleven claimed a state of "perfect health" for the previous two years.

*Modified Form of Immunization.*—Our 101 rheumatic cardiac patients who were treated in the course of the past eight years appear to have derived considerable benefit from active immunization with the hemolytic streptococcus toxin, as present and past records show, but we have been

acutely aware of the cumbersomeness of this form of treatment. It was a burden on the patient, who was required to pay about thirty-eight visits in two years to the clinic, and on the physicians who had to limit themselves to the care of a small group of treated, control, and follow-up patients because of their frequent visits. For a long time we were casting about for a modified form of N. Y. 5 strain which would retain the virtues of crude toxin in protecting the patients against recurrences of acute rheumatic fever, yet would shorten the period of immunization without producing a general or even a severe local reaction. The New York Board of Health informed us that, so far, the hemolytic streptococcus has not lent itself to the production of a toxoid but recommended that we turn to Milton V. Veldee, surgeon of the U. S. Public Health Service, who successfully used a tannic acid precipitated toxin of the N. Y. 5 strain of hemolytic streptococcus in immunizing several thousand public school children against scarlet fever. Since Veldee<sup>4</sup> used the same strain as was used by us, we decided to try his modified toxin with a new group of patients. We estimated that we had been giving to each of our patients, in the course of two years, 35,000 skin-test doses hypodermically of the crude toxin of N. Y. 5 streptococcus. It appeared reasonable to give the same amount of modified toxin of N. Y. 5 in four intradermal inoculations three weeks apart, and to repeat the third dose every six months. The modified toxin was graduated as follows: 5,000, 8,000, 10,000, and 12,000 skin-test doses.

In September, 1940, we started to inoculate forty-two new rheumatic cardiac patients at the New York Post-Graduate Hospital, and, in January, 1941, twenty-nine more patients at the City Hospital by this "short method." The patients and their relatives were pleased by the prospect of a brief course of treatment. We followed Veldee's practice of giving the intradermal inoculations of 0.1 c.c. into the triceps surface of the arm, where the puncture is covered by a sleeve, and the usually mild local reaction does not attract the attention of the patient and others.

This is a preliminary report covering nine months of observation of forty-two patients at the Cardiac Research Clinic at the New York Post-Graduate Hospital. We mention only briefly the group of twenty-nine patients at the City Hospital, for we feel they have not been observed long enough to justify a detailed report.

The 1940 to 1941 control group served for comparison with this new group of patients at the New York Post-Graduate Hospital. Sixteen of the new patients who received the modified treatment belonged to the control group in 1939 to 1940 and have been placed in the "short treatment" group either because they asked for it, or because they were so ill that we wished especially to include them in the group.

TABLE VI

COMPARISON BETWEEN PATIENTS RECEIVING THE MODIFIED TREATMENT AND CONTROL PATIENTS

|   | TREATED              |               | CONTROL              |               |
|---|----------------------|---------------|----------------------|---------------|
| No. of patients   | 42                   |               | 33                   |               |
| Sex   | 27 males; 15 females |               | 17 males; 16 females |               |
| Av. age (yr.)   | 10.9                 |               | 12.1                 |               |
| No. of reported colds per child                         | 1.45                 |               | 2.9                  |               |
| Mean gain in weight (lb.)                               | 7.5                  |               | 7.9                  |               |
| Abdominal symptoms                                      |                      |               |                      |               |
| +   | 8                    |               | 4                    |               |
| ++  | 5                    |               | 4                    |               |
| +++   | 2                    |               | 5                    |               |
| Pallor  |                      |               |                      |               |
| +   | 2                    |               | 3                    |               |
| ++  | 5                    |               | 1                    |               |
| +++   | 4                    |               | 12                   |               |
| Epistaxis   |                      |               |                      |               |
| +   | 3                    |               | 3                    |               |
| ++  | 1                    |               | 4                    |               |
| +++   | 3                    |               | 0                    |               |
| Rheumatic pains   |                      |               |                      |               |
| +   | 9                    |               | 3                    |               |
| ++  | 4                    |               | 3                    |               |
| +++   | 3                    |               | 14                   |               |
| Cardiac symptoms  |                      |               |                      |               |
| +   | 5                    |               | 5                    |               |
| ++  | 1                    |               | 1                    |               |
| +++   | 3                    |               | 10                   |               |
| Headaches   |                      |               |                      |               |
| +   | 11                   |               | 1                    |               |
| ++  | 4                    |               | 1                    |               |
| +++   | 3                    |               | 11                   |               |
| Twitching   |                      |               |                      |               |
| +   | 3                    |               | 2                    |               |
| ++  | 2                    |               | 2                    |               |
| +++   | 3                    |               | 4                    |               |
| No. of attacks of rheumatic fever, carditis, and chorea | 0                    |               | 11, or 33%           |               |
| Deaths  | 0                    |               | 3                    |               |
| Mean laboratory data:                                   |                      |               |                      |               |
| E.S.R. (mm. per hr.)                                    | 9                    |               | 17                   |               |
| Hemoglobin (%)  | 76.1                 |               | 73.2                 |               |
| Nonfilamented neutrophils (%)                           | 8.33                 |               | 10.5                 |               |
| Platelets per cu. mm.                                   | 210,000              |               | 192,000              |               |
| Estimation of patient's condition:                      | <i>Fall</i>          | <i>Spring</i> | <i>Fall</i>          | <i>Spring</i> |
|   | (1940)               | (1941)        | (1940)               | (1941)        |
| Excellent   | 5                    | 20            | 10                   | 8             |
| Very good   | 8                    | 9             | 4                    | 2             |
| Good  | 7                    | 7             | 5                    | 4             |
| Av.   | 10                   | 3             | 5                    | 4             |
| Fair  | 5                    | 1             | 5                    | 4             |
| Poor  | 7                    | 2             | 4                    | 11            |

Symbols: +, occurred once; ++, occurred twice; +++, occurred more than twice.

Of the forty-two patients, fifteen were girls and twenty-seven boys. Their average age was the lowest among all the groups, namely, 10.9 years. The number of reported colds per child was also the lowest, viz., 1.45. The mean gain in weight per child was 7.5 pounds in nine months. There were few subacute rheumatic symptoms. Two patients complained of frequent abdominal distress; three, of rheumatic pains on more than two occasions; three, of frequent headaches; and three, of twitching. Not a single patient developed a fresh attack of rheumatic fever, but one who has both congenital and rheumatic heart disease and is chronically decompensated, and another who, at the outset, had moderate chorea, showed no improvement. The blood picture was normal. A glance at Table VI will show the contrast between this group and the thirty-three control children.

These results appear to us by far the most encouraging, especially because we went to great pains in September, 1940, to get a group of children who were the most ill during the preceding winter and especially during spring. The control group of thirty-three patients in September, 1940, contained only five severe cardiac patients, whereas the newly treated group contained thirteen. In the control group, thirteen instances of acute rheumatic fever occurred, with three deaths, but, as stated, in the treated group not a single new attack developed, although two patients showed no improvement.

Twenty-nine patients have been treated by the same method at the City Hospital pediatric clinic since the beginning of 1941. Of those, thirteen were boys and sixteen girls. The average age was 11.5 years. Their mean gain in weight was 3.1 pounds for six months, which would be modest enough if one did not take into account that the patients at the City Hospital come from among New York's poorest. However, only one child developed an attack of chorea. The rest remained well and had few minor complaints, and their sedimentation rates and blood cell counts were normal.

#### COMMENT

Twice before, we have recorded the satisfactory results of immunization of ambulatory patients suffering from rheumatic heart disease. Sixty-six carefully controlled patients received graduated injections of hemolytic streptococcus filtrate prior to 1939. This paper discusses the condition of thirty-five more rheumatic cardiac children who have received a two-year course of treatment since then. After eight years of trial of this method, we feel that it is fair to say that the treated patients have shown a striking reduction in the number of attacks of acute rheumatic fever, and a marked general improvement in health. Many formerly treated patients have been observed for as long as six



years since the injections were discontinued, and their health has remained materially better than that of untreated patients. If a hemolytic streptococcus toxin has been able to confer immunity upon them, that immunity is of long duration. Our bacteriologic studies show that treated patients would get upper respiratory infections, but they would be of short duration and seldom would be followed by a flare-up of rheumatic fever.

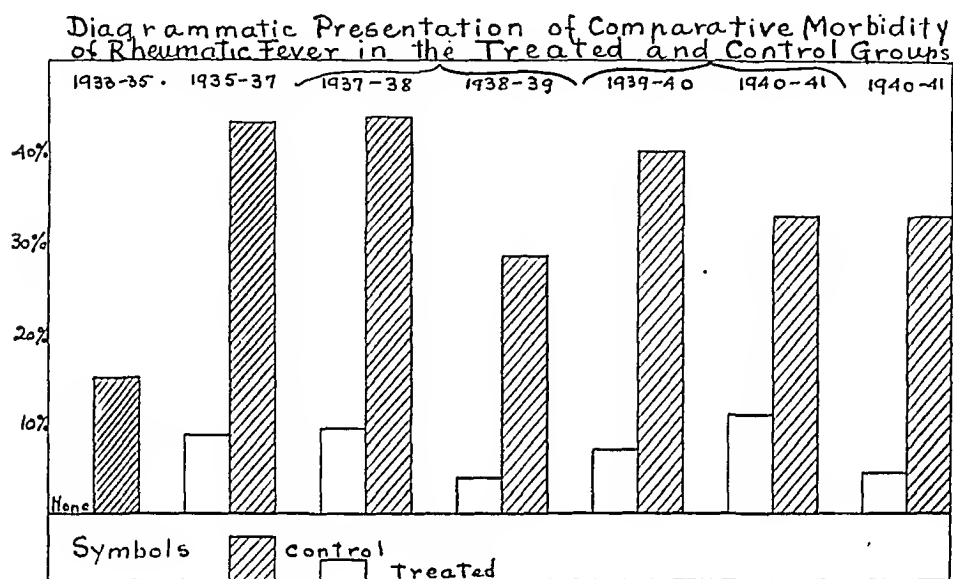


Fig. 1.

However, the drawbacks of this form of protracted prophylactic treatment are obvious, and we have tried an abbreviated method of immunization on forty-two children, giving them the total number of skin-test doses in four (instead of thirty-eight) inoculations intradermally, three weeks apart. The N. Y. 5 toxin has been attenuated with tannic acid, and the intradermal route allows a slow absorption of the toxin. Reactions have been only local, but in a number of highly sensitized children they were as large as 5 to 7 cm. in diameter. The only subjective symptom was itching twenty-four hours later. A number, but unfortunately not all, of the patients received preliminary skin tests for determining sensitivity with one, two, and five skin-test doses of highly purified *Streptococcus hemolyticus* toxin and were retested a month after the fourth inoculation. However, the entire group was skin-tested after the treatment. We shall report on the skin test in another year and hope by that time to treble the number of patients who will have received this abbreviated form of immunization. Almost everyone in this group received the first semiannual inoculation in May or June, 1941. Only prolonged observation will show whether the results of this form of treatment are as lasting as those of the protracted treatment.

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## THE INDUCED ANOXEMIA TEST

### A STUDY BY AGE GROUPS

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**A**NOXEMIA as a result of some derangement of the gaseous interchange mechanism or a natural diminution of available atmospheric oxygen, as at high altitudes, has attracted an increasing amount of attention in recent years. Among the earliest observations of altitude effects were those of the Pikes Peak Expedition of 1911, when Schneider, Henderson, Haldane, and Douglas spent several weeks at the summit of this 14,110-foot mountain. These men were already well-trained physiologists; they were well equipped; and their observations remain the foundation for all subsequent investigation on the effects of anoxemia.

Although Paul Bert had, some forty years before, called attention to compensatory changes which occur in the blood as a result of residence at a high altitude, it remained for these observers to furnish more accurate data concerning blood changes at high altitudes, as compared to sea level, in the same person, as well as changes in the oxygen carrying capacity of the blood and in the respiratory mechanism, and changes (of especial importance in relation to the subject of this paper) in the circulatory apparatus. Later these and other investigators compared their observations with those obtained by placing a person in a chamber in which the amount or percentage of oxygen could be controlled (low pressure chamber), under conditions simulating those encountered at altitudes ranging from sea level to 22,000 ft. Somewhat later there was introduced a rebreathing apparatus by means of which the subject breathes the air from a tank, thereby causing a progressive decrease of oxygen. Since the carbon dioxide of the expired air is removed by an absorbent, it was thought to be eliminated as a factor in the test, but there appears to be some uncertainty regarding this point.

The results of these various investigations showed that, regardless of the method employed, the effects of low oxygen tension are the same whether they are induced by altitude or dilution, either immediate or slowly induced, and that barometric pressure, per se, is not the cause of these changes, but that such changes are due to variations in the oxygen tension, and that, even at such altitudes as that of the summit of Pikes Peak, all evidence of altitude effects can be eliminated by the

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administration of an amount of oxygen sufficient to simulate sea level conditions. This work early attracted the attention of those who were especially interested in the effects of extremely rapid and often repeated changes in altitude, such as are encountered in aviation. Credit should be given to members of our air service for numerous and valuable contributions.

We have thus far mentioned only the application of these studies to normal men, namely, the effects of variously induced anoxemia states. About fifteen years ago (1925 and 1926), reports of the effects of anoxemia on the heart began to appear in medical literature. It was pointed out by Resnik<sup>1</sup> that, under conditions of anoxemia, changes in cardiac impulse conduction occur and that a damaged heart, when subjected to anoxemia, may early exhibit functional disturbances which will appear only in the presence of a more profound anoxemia in the normal heart.

The theory advanced by Danielopolu,<sup>2</sup> namely, that angina pectoris is due to a disproportion between the flow of blood in the coronary vessels, on the one hand, and the work of the heart, on the other, furnishes a basis for the test under consideration. He pointed out that, even if a heart has normal arteries, and the demands are great enough, coronary artery insufficiency may become so marked as to lead to angina, and that, when these arteries are diseased, lesser demands will bring on the anginal syndrome. The author presented this explanation of angina but did not offer satisfactory evidence that there may be coronary insufficiency in the presence of normal coronary arteries. This evidence appeared much later in the work of Rothseild and Kissin,<sup>3</sup> Levy, et al.,<sup>4</sup> and others.

At about this time (1928), Keefer and Resnik<sup>5</sup> expressed the belief that angina pectoris is always due to anoxemia of the myocardium and that there is a great difference in the response of different hearts to anoxemia, which is dependent upon varying ability to compensate, and that infarction depends upon the rapidity of occlusion and the richness of the previously existing anastomoses; both factors determine the degree of local anoxemia attained.

In the past decade, numerous workers have presented evidence of changes in the electrocardiogram as a result of myocardial ischemia induced by ligation of coronary arteries,<sup>6-8, 39</sup> by the local effect of vasoconstrictors,<sup>7</sup> and, finally, by brief attacks of angina pectoris.<sup>9, 10</sup> In each instance, the changes which occur are in many respects comparable to those which follow occlusion of one of the coronary arteries, namely, alterations in the amplitude or direction of the T waves and shifts in the position and form of the S-T segments. Experimental proof<sup>10</sup> was presented that myocardial ischemia is responsible for these changes, and that this localized ischemia is due to coronary artery insufficiency, which is either functional (due to an excessive demand for

blood flow) or organic (due to some form of narrowing of the coronary vessels). Parallel clinical observations<sup>11</sup> demonstrated, in addition to the above-mentioned electrocardiographic changes in response to anoxemia induced by various means, that it is also "possible to reproduce the pain of angina pectoris in susceptible subjects" and that the coronary circulation, which is normally adequate, becomes inadequate during anoxemia. Pain in other muscles under anoxic conditions was studied. It was demonstrated<sup>12</sup> that exercise of the forearm under anoxic conditions will induce pain which disappears when the blood is flushed with oxygen and that no pain occurs if the oxygen supply is adequate. The suggestion was advanced that the pain of angina may be due to the muscular activity of the heart in the presence of oxygen deficiency. In a recent study,<sup>13</sup> after ligation of a coronary artery and recovery therefrom, animals were subjected to induced anoxemia. An increase in the RS-T deviation which was already present as a result of the ligation was observed in twelve of fourteen animals; this seemed to justify the use of the test in the differential diagnosis of coronary insufficiency.

In summary, it has been shown that attacks of anginal pain induced by anoxemia are identical with spontaneous attacks, that anoxemia is at least in part responsible for the pain of angina pectoris, and that, associated with either spontaneous or induced attacks, there are characteristic changes in the electrocardiogram.<sup>4, 9, 10, 14</sup> Finally, it has been suggested that these responses to induced anoxemia can be employed in the diagnosis of impairment of the coronary circulation.<sup>4</sup>

In February, 1939, Levy, Bruenn, and Russell<sup>4</sup> presented a clinical test for coronary insufficiency which was based upon the foregoing evidence. In a subsequent paper, Levy and his associates modified their criteria somewhat, but, in the main, substantiated their earlier report. Some of their critics, including the senior author, entertained some hesitancy regarding the acceptance of their criteria, for it appeared that (1) these criteria had been based upon an insufficient number of normal subjects, and (2) there was nothing in the report of these observers to indicate that they had made a comparative study of the response to induced anoxemia at various ages. It seemed rather probable that persons of widely varying ages might not respond similarly to a given stress; that is, that the normal response at fifty years, and above, would probably differ from that observed in young persons. With this in mind, apparently, May<sup>35</sup> studied the effect of anoxemia in a group of fifty normal persons and twenty patients with various types of heart disease. He used the rebreathing method, the results of which we believe are not quite comparable to those obtained with the dilution method previously employed by Levy, and later by Levy and ourselves, in which the expired carbon dioxide is passed out immediately, thus preventing any side effects of carbon dioxide, and, at the same time, ensuring a constant percentage of oxygen, regardless of the duration

of the test. In the rebreathing method employed by May, the subject depletes the oxygen in the air until it reaches the point of anoxemia. In our method the subject has his full oxygen reserve at the beginning of the test; in the rebreathing method the oxygen reserve is steadily depleted. In rebreathing it appears impossible to know the point at which the loss of reserve passes over into the anoxemic state, and it is therefore impossible to ascertain the time element with any degree of accuracy. The duration of May's tests ranged from seven to fourteen minutes and electrocardiograms were taken before, during, and at approximately three minutes after the test. It would seem that some of his records may have been taken before anoxemia developed. In rebreathing, anoxemia is brought about by metabolic utilization of oxygen, the rate of which varies with the weight, degree of mental excitement, and age of the subject. It also varies according to the length of period of rest and whether or not food has been taken. It is not possible, therefore, for May to state from his work the degree of anoxemic stress to which the subject was exposed, but it is reasonable to assume that, because of the higher average metabolic rate in the young, the anoxemic stress in this group was greater. We believe his observation that "the effect of oxygen deficiency, as measured by diminution in the height of the T waves, lessens considerably with advancing age" is unwarranted in view of the above-mentioned considerations. We feel, therefore, that May's comparison of the responses to anoxemia at various ages is not valid. Because of these apparent inaccuracies in the rebreathing method, we instituted in the summer of 1939 a study of the clinical and electrocardiographic response to induced anoxemia, employing the dilution method previously described by Levy, et al.<sup>4</sup>

TABLE I

OXYGEN PERCENTAGES EMPLOYED, WITH ALTITUDE EQUIVALENTS<sup>50</sup>

|                                   |                        |                      |
|-----------------------------------|------------------------|----------------------|
| 10% oxygen at sea level           | =                      | altitude 20,800 ft.  |
| 10% oxygen at 5,420 ft. (Denver)  | = 8.29% at sea level = | altitude 25,900 ft.  |
| 12% oxygen at 5,420 ft. (Denver)  | = 9.95% at sea level = | altitude 20,200 ft.  |
| 8.6% oxygen at 5,420 ft. (Denver) | = 7.13% at sea level = | altitude 31,000 ft.* |

\*The altitude equivalent for 8.6 per cent oxygen can only be approximated as the FitzGerald Chart No. 2 (p. 253) employed does not permit direct reading of the altitude, that is, a curved line must be extended and estimation made therefrom.

The gas mixture in our tanks approximated 10 per cent oxygen and 90 per cent nitrogen, except in the study of two small groups which are presented separately, in which the percentages of oxygen were 12 and, by error, 8.5, respectively. Actually, these are equivalent to sea level, as shown in Table I. The approximate altitude represented by these percentages is also shown.

These percentage figures are derived by use of the following formula:

$$\frac{\times (\text{sea level equivalent})}{630} = \frac{\% \text{ oxygen in tank}}{760}$$

Average barometric pressure at sea level, 760; average barometric pressure at Denver, 630.

|             |                                     |              |
|-------------|-------------------------------------|--------------|
| 10% oxygen  | $\frac{x}{630} = \frac{0.10}{760}$  | $x = 8.29\%$ |
| 12% oxygen  | $\frac{x}{630} = \frac{0.12}{760}$  | $x = 9.95\%$ |
| 8.6% oxygen | $\frac{x}{630} = \frac{0.086}{760}$ | $x = 7.13\%$ |

Most of the observations relative to the effect of induced anoxemia reported by Levy and others were made under anoxemia produced by 10 per cent oxygen mixtures. It is well recognized that residence at an altitude no higher than that of Denver confers some adaptation to the diminished oxygen content of the air. This varies with the person, but we feel that it is probably sufficient to compensate for the difference in oxygen percentage observed when the gas is passed from the pressure tank into a rubber bag, and thus exposed to the low partial pressure of this altitude. Therefore, since we wished to make comparable observations, although we recognize this difference in partial pressure between sea level and Denver, we have employed mainly a 10 per cent oxygen mixture. *Throughout this paper we shall state the percentage of oxygen existing in the tanks, rather than that in the bag immediately before inhalation.*

In the early stage of this investigation we encountered some difficulty in obtaining a dependable and fairly constant oxygen-nitrogen mixture. We learned that a gas analysis of each tank was required because a permissible error of 1 per cent in the oxygen percentage (our standard) might be exceeded by the manufacturers. Our experience teaches that a producer's guarantee should always be supplemented by a gas analysis.

As stated previously, we felt that a comparison of the response to anoxemia at various ages might show a sufficient difference to be of clinical importance; that is, we suspected that the response of the normal person in the "coronary" age might differ perceptibly from that of the man in the third and fourth decades. Since no published studies, save those of May, which have already been discussed, indicated that such a comparison had been made, we proceeded to select subjects for this test in groups according to age by decades.

#### SELECTION OF CASES

For the most part, the patients, particularly those 41 to 50 and 51 to 60 years old, were selected from the outpatient medical service; those who were 21 to 30 and 31 to 40 were mainly medical students and nurses. All subjects were free of any cardiovascular symptoms or signs, pulmonary symptoms, and abnormal electrocardiographic changes.

## PROCEDURE

In each instance the subject rested in bed for one hour prior to the start of the test to insure near-basal conditions. With the apparatus in place beside the bed, the purpose of the test was re-explained, together with some of the symptoms which might ensue, that is, numbness and tingling of the extremities, palpitation, precordial pain, and "lightness in the head." The subject was cautioned that any severe pain which developed should be localized with the right hand; any "short-windedness" or "feeling as of running" could best be minimized by breathing more rapidly or more deeply, but at all times *regularly*. It was emphasized that the "air mixture" bag (10 per cent oxygen and 90 per cent nitrogen) would always be full and the supply ample. The more slowly and simply these details were explained to each subject, the less apprehensive and more confident he became, and discontinuation of the test because of discomfort or "nervousness" was minimized.

The well-moistened mouthpiece was then adjusted comfortably between the lips and teeth, and the nose clip was attached; both were tested to insure a "closed system." A control electrocardiogram was then taken, after which the subject was given the gas mixture from the inflated bag instead of room air.

The blood pressure, pulse rate, and electrocardiogram were recorded every five minutes. At the end of twenty minutes, 100 per cent oxygen was given for one minute, after which the blood pressure, pulse rate, and electrocardiogram were again recorded. The apparatus was then removed, and the blood pressure, pulse rate, and electrocardiogram were obtained at five- and ten-minute intervals. Throughout the test the lips and mouthpiece were kept moist to insure the maintenance of a "closed system." At two- to three-minute intervals the patient was tested for response to auditory and visual stimuli, and these were recorded; the latter consisted of a request to look at the observer's forehead, and the promptness of response, as well as power of concentration, was recorded in terms of "good," "poor," or "no response." At varying intervals the subject was reassured that the test was proceeding satisfactorily.

If the subject developed severe precordial pain, undue restlessness, clonic muscle contractions, or unresponsiveness to auditory or visual stimuli at any time during the test, 100 per cent oxygen was given for one minute, the blood pressure and pulse rate were recorded, and an electrocardiogram was taken. Following this, while the subject was breathing room air, the electrocardiogram, blood pressure, and pulse rate were recorded at two succeeding five-minute intervals.

CHANGES IN THE ELECTROCARDIOGRAM OF THE NORMAL SUBJECT CAUSED BY  
BREATHING A MIXTURE OF 10 PER CENT OXYGEN  
AND 90 PER CENT NITROGEN

The changes in the first age group (21 to 30 years) are graphically shown in Fig. 1, which represents the average of the exact measurements of the height or depression of the RS-T segment and the T waves. In this series there were fifty normal subjects. For the reader who is interested in greater detail than can be shown in graphic form we present Tables II and III, which give the average measurements. A study of Fig. 1 and Tables II and III shows that in the normal subject there is an early and prompt depression of all T waves, particularly  $T_3$ , which regularly becomes flat or nearly so, and that with this change there is a deviation of the RS-T segment from the isoelectric line; both



changes reach their maximum at the end of the twenty-minute exposure to the 10 per cent oxygen mixture.

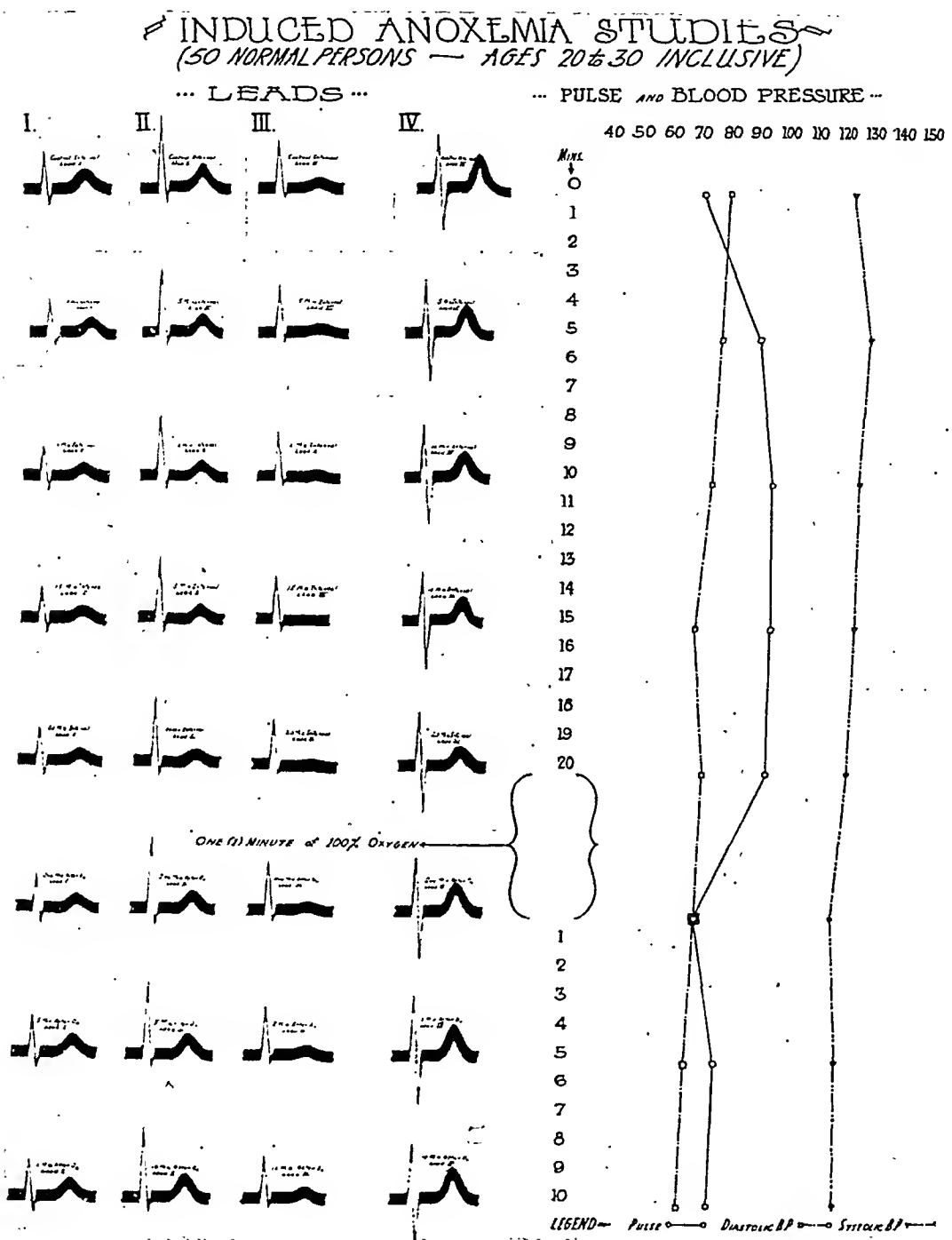


Fig. 1.

In our control electrocardiograms, taken before the administration of the 10 per cent oxygen mixture, we encountered slight left axis deviation in about the same frequency in all age groups. In all instances in which this occurred it was consistent with the habitus of the subject, and, since we find that anoxemia causes no consistent or

TABLE II  
THE RS-T INTERVAL

| AGE<br>(YR.) | DATA | CONTROL | MINUTES OF 10% O <sub>2</sub> 90% N |         |         |         | MINUTES AFTER 100% O <sub>2</sub> |        |         |
|--------------|------|---------|-------------------------------------|---------|---------|---------|-----------------------------------|--------|---------|
|              |      |         | 5 MIN.                              | 10 MIN. | 15 MIN. | 20 MIN. | 1 MIN.                            | 5 MIN. | 10 MIN. |

*Lead I*

|          |      |      |      |      |      |      |      |     |     |
|----------|------|------|------|------|------|------|------|-----|-----|
| 21 to 30 | Max. | +1.0 | +1.0 | +0.5 | +0.5 | 0.0  | 0.0  | 0.0 | 0.0 |
|          | Av.  | +0.1 | 0.0  | 0.0  | 0.0  | -0.1 | 0.0  | 0.0 | 0.0 |
|          | Min. | 0.0  | 0.0  | -0.5 | -0.5 | -1.0 | -0.5 | 0.0 | 0.0 |
| 31 to 40 | Max. | 0.0  | 0.0  | 0.0  | 0.0  | 0.0  | 0.0  | 0.0 | 0.0 |
|          | Av.  | 0.0  | 0.0  | 0.0  | -0.1 | 0.0  | 0.0  | 0.0 | 0.0 |
|          | Min. | 0.0  | 0.0  | -0.5 | -1.0 | -0.5 | 0.0  | 0.0 | 0.0 |
| 41 to 50 | Av.  | 0.0  | 0.0  | 0.0  | 0.0  | 0.0  | 0.0  | 0.0 | 0.0 |
| 51 to 60 | Max. |      |      |      | 0.0  | 0.0  | 0.0  |     |     |
|          | Av.  | 0.0  | 0.0  | 0.0  | -0.1 | -0.1 | -0.1 | 0.0 | 0.0 |
|          | Min. |      |      |      | -1.0 | -1.0 | -1.0 |     |     |

*Lead II*

|          |      |      |      |      |      |      |      |      |      |
|----------|------|------|------|------|------|------|------|------|------|
| 21 to 30 | Max. | +2.0 | +2.0 | +1.0 | +1.0 | +1.0 | +0.5 | +1.0 | +1.0 |
|          | Av.  | +0.2 | +0.1 | +0.0 | -0.1 | -0.2 | -0.0 | +0.1 | +0.1 |
|          | Min. | -0.5 | -1.0 | -1.0 | -1.0 | -2.0 | -0.5 | 0.0  | 0.0  |
| 31 to 40 | Max. | +1.0 | +0.5 | +0.5 | 0.0  | 0.0  | 0.0  | 0.0  | +0.5 |
|          | Av.  | +0.1 | 0.0  | -0.1 | -0.3 | -0.5 | -0.1 | 0.0  | 0.0  |
|          | Min. | 0.0  | -1.0 | -1.0 | -2.0 | -1.0 | -1.0 | 0.0  | -0.5 |
| 41 to 50 | Max. | +1.0 | +0.5 | 0.0  | 0.0  | 0.0  | 0.0  | 0.0  | +1.0 |
|          | Av.  | +0.1 | -0.1 | -0.2 | -0.6 | -0.4 | 0.0  | 0.0  | 0.0  |
|          | Min. | -0.5 | -1.0 | -1.0 | -2.0 | -1.5 | -1.0 | -0.5 | 0.0  |
| 51 to 60 | Max. | +1.0 | +1.0 | +1.0 | 0.0  | +0.5 | +1.0 | +0.5 | +0.5 |
|          | Av.  | 0.0  | 0.0  | -0.1 | -0.2 | -0.3 | 0.0  | 0.0  | 0.0  |
|          | Min. | -0.5 | -1.0 | -1.5 | -1.0 | -1.0 | -0.5 | -0.5 | 0.0  |

*Lead III*

|          |      |      |      |      |      |      |      |      |      |
|----------|------|------|------|------|------|------|------|------|------|
| 21 to 30 | Max. | +0.5 | +0.5 | +1.0 | +0.5 | +0.5 | +0.5 | +0.5 | +1.0 |
|          | Av.  | +0.1 | +0.1 | 0.0  | -0.2 | -0.3 | 0.0  | 0.0  | 0.0  |
|          | Min. | -0.5 | -0.5 | -1.0 | -1.0 | -1.0 | -0.5 | -0.5 | 0.0  |
| 31 to 40 | Max. | +0.5 | +0.5 | 0.0  | 0.0  | 0.0  | +0.5 |      |      |
|          | Av.  | 0.0  | 0.0  | -0.1 | -0.2 | -0.3 | 0.0  | 0.0  | 0.0  |
|          | Min. | -0.5 | -0.5 | -1.0 | -1.0 | -1.5 | -1.0 |      |      |
| 41 to 50 | Max. | +0.5 | 0.0  | 0.0  | 0.0  | 0.0  | 0.0  |      |      |
|          | Av.  | 0.0  | 0.0  | -0.1 | -0.1 | -0.1 | 0.0  | 0.0  | 0.0  |
|          | Min. | 0.0  | -1.0 | -1.0 | -2.0 | -1.0 | -0.5 |      |      |
| 51 to 60 | Max. | +0.5 | +0.5 | +0.5 | 0.0  | +0.5 | +0.5 | +0.5 | +0.5 |
|          | Av.  | +0.2 | 0.0  | -0.1 | -0.1 | -0.2 | 0.0  | 0.0  | 0.0  |
|          | Min. | -0.5 | -1.0 | -1.0 | -1.0 | -1.0 | -0.5 | -0.5 | 0.0  |

*Lead IV*

|          |      |      |      |      |      |      |      |      |      |
|----------|------|------|------|------|------|------|------|------|------|
| 21 to 30 | Max. | +2.0 | +1.5 | +2.0 | +1.5 | +2.0 | +1.0 | +1.0 | +2.0 |
|          | Av.  | +0.2 | +0.1 | -0.1 | -0.1 | 0.0  | +0.1 | +0.1 | +0.1 |
|          | Min. | 0.0  | 0.0  | -1.0 | -1.0 | -3.0 | 0.0  | 0.0  | 0.0  |
| 31 to 40 | Max. | +2.0 | +1.0 | 0.0  | +1.0 | +0.5 | +1.0 | +1.0 | +1.0 |
|          | Av.  | +0.2 | +0.1 | 0.0  | 0.0  | 0.0  | +0.1 | +0.1 | +0.1 |
|          | Min. | 0.0  | 0.0  | -0.5 | -1.0 | -0.5 | 0.0  | 0.0  | 0.0  |
| 41 to 50 | Max. | +1.0 | +1.0 | +1.0 | +1.0 | +1.0 | +1.0 | +1.0 | +1.0 |
|          | Av.  | 0.0  | 0.0  | 0.0  | 0.0  | -0.5 | 0.0  | 0.0  | 0.0  |
|          | Min. | 0.0  | -0.5 | -1.0 | -1.0 | -1.0 | -0.5 | 0.0  | 0.0  |
| 51 to 60 | Max. | +1.0 | +1.0 | +1.0 | +1.0 | +1.0 | +1.0 |      |      |
|          | Av.  | +0.1 | +0.1 | 0.0  | 0.0  | -0.1 | 0.0  | 0.0  | 0.0  |
|          | Min. | 0.0  | 0.0  | -0.5 | -1.0 | -1.5 | -0.5 |      |      |

TABLE III  
THE T WAVE

| AGE<br>(YR.) | DATA | CONTROL | MINUTES OF 10% O <sub>2</sub> 90% N |         |         |         | MINUTES AFTER 100% O <sub>2</sub> |        |         |
|--------------|------|---------|-------------------------------------|---------|---------|---------|-----------------------------------|--------|---------|
|              |      |         | 5 MIN.                              | 10 MIN. | 15 MIN. | 20 MIN. | 1 MIN.                            | 5 MIN. | 10 MIN. |
| Lead I       |      |         |                                     |         |         |         |                                   |        |         |
| 21 to 30     | Max. | +5.0    | +4.0                                | +3.5    | +3.5    | +3.0    | +4.5                              | +4.0   | +5.0    |
|              | Av.  | +2.5    | +1.7                                | +1.4    | +1.2    | +1.2    | +1.6                              | +2.3   | +2.4    |
|              | Min. | +1.0    | +0.5                                | -0.5    | -0.5    | -0.5    | 0.0                               | +1.0   | +1.0    |
| 31 to 40     | Max. | +5.0    | +2.0                                | +2.5    | +3.0    | +2.0    | +4.0                              | +5.0   | +6.0    |
|              | Av.  | +2.2    | +1.4                                | +0.9    | +0.8    | +0.6    | +1.4                              | +1.9   | +2.0    |
|              | Min. | +1.0    | +0.5                                | -0.5    | -1.5    | -1.0    | 0.0                               | +0.5   | +1.5    |
| 41 to 50     | Max. | +3.0    | +2.0                                | +2.0    | +1.0    | +1.0    | +3.0                              | +3.0   | +4.0    |
|              | Av.  | +1.5    | +1.0                                | +1.0    | +0.5    | +0.2    | +1.2                              | +1.5   | +1.6    |
|              | Min. | +0.5    | 0.0                                 | 0.0     | -1.0    | -2.0    | -0.5                              | +0.5   | +0.5    |
| 51 to 60     | Max. | +4.5    | +3.0                                | +3.0    | +3.0    | +3.0    | +3.0                              | +4.0   | +4.0    |
|              | Av.  | +2.0    | +1.2                                | +1.0    | +0.4    | +0.7    | +1.1                              | +2.2   | +2.1    |
|              | Min. | +0.5    | 0.0                                 | -0.5    | -1.0    | -1.5    | -1.0                              | +0.5   | +0.5    |

|                |      |      |      |      |      |      |      |      |      |
|----------------|------|------|------|------|------|------|------|------|------|
| <i>Lead II</i> |      |      |      |      |      |      |      |      |      |
| 21 to 30       | Max. | +8.5 | +6.0 | +4.5 | +4.5 | +5.0 | +6.0 | +6.0 | +6.0 |
|                | Av.  | +3.3 | +2.1 | +1.7 | +1.5 | +1.2 | +2.2 | +2.9 | +3.2 |
|                | Min. | +0.5 | -1.5 | -2.0 | -3.5 | -3.0 | -1.5 | +1.0 | +1.0 |
| 31 to 40       | Max. | +5.0 | +2.0 | +3.0 | +2.0 | +4.0 | +4.0 | +4.5 | +5.0 |
|                | Av.  | +3.1 | +1.7 | +1.1 | +1.0 | +0.9 | +1.8 | +2.6 | +2.8 |
|                | Min. | +2.0 | +0.5 | -2.0 | -2.0 | -2.5 | -2.0 | +1.0 | +2.0 |
| 41 to 50       | Max. | +6.0 | +4.0 | +3.0 | +3.0 | +2.5 | +5.0 | +5.0 | +5.0 |
|                | Av.  | +3.2 | +1.6 | +1.3 | +1.3 | +1.3 | +2.2 | +3.0 | +3.0 |
|                | Min. | +1.0 | -0.5 | -2.0 | -3.0 | -3.0 | -1.5 | +1.0 | +2.0 |
| 51 to 60       | Max. | +5.5 | +4.5 | +4.0 | +4.0 | +3.5 | +6.0 | +5.0 | +7.0 |
|                | Av.  | +3.2 | +2.2 | +1.9 | +1.7 | +1.7 | +2.6 | +2.9 | +3.1 |
|                | Min. | +0.5 | -1.0 | -1.0 | -1.0 | -1.0 | -1.0 | -1.5 | -1.0 |

|                 |      |      |      |      |      |      |      |      |      |
|-----------------|------|------|------|------|------|------|------|------|------|
| <i>Lead III</i> |      |      |      |      |      |      |      |      |      |
| 21 to 30        | Max. | +4.0 | +4.0 | +2.5 | +2.5 | +2.5 | +3.5 | +4.0 | +4.0 |
|                 | Av.  | +1.0 | +0.7 | +0.2 | -0.2 | -0.2 | +0.5 | +0.9 | +1.0 |
|                 | Min. | -2.0 | -2.0 | -2.0 | -3.0 | -3.0 | -2.0 | -1.5 | -1.0 |
| 31 to 40        | Max. | +2.0 | +2.0 | +2.0 | +2.0 | +3.0 | +2.0 | +2.0 | +3.0 |
|                 | Av.  | +0.9 | +0.2 | 0.0  | 0.0  | 0.0  | +0.4 | +0.8 | +1.8 |
|                 | Min. | -1.5 | -2.0 | -3.0 | -3.0 | -2.5 | -1.5 | -2.0 | -2.0 |
| 41 to 50        | Max. | +4.0 | +3.0 | +2.0 | +2.0 | +2.0 | +3.0 | +3.0 | +4.0 |
|                 | Av.  | +1.6 | +0.9 | +0.2 | +0.2 | +0.2 | +1.0 | +1.4 | +1.6 |
|                 | Min. | -1.0 | -1.0 | -1.0 | -2.0 | -1.5 | -1.0 | 0.0  | 0.0  |
| 51 to 60        | Max. | +6.0 | +3.0 | +5.0 | +2.0 | +3.5 | +3.0 | +3.5 | +3.0 |
|                 | Av.  | +1.2 | +1.3 | +0.8 | +0.7 | +0.8 | +1.2 | +1.1 | +1.1 |
|                 | Min. | -1.0 | -0.5 | -0.5 | -1.0 | -0.5 | -0.5 | -1.0 | -0.5 |

|                |      |       |       |      |      |      |       |       |       |
|----------------|------|-------|-------|------|------|------|-------|-------|-------|
| <i>Lead IV</i> |      |       |       |      |      |      |       |       |       |
| 21 to 30       | Max. | +9.0  | +10.0 | +9.0 | +9.0 | +6.0 | +9.0  | +8.0  | +11.0 |
|                | Av.  | +5.0  | +4.1  | +3.6 | +3.1 | +2.7 | +4.0  | +4.6  | +4.7  |
|                | Min. | +2.0  | 0.0   | -1.0 | -2.0 | -2.5 | -0.5  | +1.0  | 0.0   |
| 31 to 40       | Max. | +8.0  | +7.0  | +7.0 | +5.0 | +6.0 | +6.0  | +7.5  | +8.0  |
|                | Av.  | +3.5  | +2.4  | +2.0 | +1.6 | +1.5 | +2.4  | +3.1  | +3.1  |
|                | Min. | +2.0  | -0.5  | -0.5 | -1.0 | -2.5 | -0.5  | +1.0  | 0.0   |
| 41 to 50       | Max. | +9.0  | +7.0  | +6.0 | +5.0 | +6.0 | +8.0  | +8.0  | +9.0  |
|                | Av.  | +3.8  | +2.1  | +1.5 | +1.0 | +1.0 | +2.0  | +3.1  | +3.5  |
|                | Min. | +1.0  | -1.5  | -3.0 | -4.0 | -4.5 | -1.5  | -1.0  | 0.0   |
| 51 to 60       | Max. | +13.0 | +11.0 | +8.0 | +8.0 | +8.0 | +10.0 | +10.0 | +11.0 |
|                | Av.  | +5.3  | +4.2  | +2.8 | +2.9 | +2.6 | +4.0  | +4.5  | +4.3  |
|                | Min. | +2.0  | +1.0  | -0.5 | -1.0 | -1.0 | +1.0  | 0.0   | 0.0   |

significant changes in the R and S waves, we have considered as of no clinical importance the presence of slight left axis deviation in an otherwise normal person of sthenic habitus.  $T_4$  showed a variable height and was higher in the fifth than the fourth decade; for this we have no explanation. Two subjects not included in our normal series showed  $T_4$  inversion in the control which was suggestive of coronary artery disease. In both, the wave became upright during anoxemia.

According to Levy, in the presence of coronary insufficiency these RS-T segment and T-wave changes become greatly exaggerated. Partial or complete reversal of T waves may occur with or without these RS-T deviations (for details, see Levy's criteria, below). Usually when the 10 per cent oxygen and 90 per cent nitrogen mixture is replaced with pure oxygen for one minute, followed by respiration of air, these changes quickly disappear, and, by the end of the ten minutes, the curve returns to the form of the control record.

Tables II and III present the average measurements of the RS-T segments and the T waves in the four age groups. In the first this represents an average of fifty cases; in the others it is twenty-five cases, for restudy of measurements obtained in the first group indicated that a sample of twenty-five cases was adequate.

In order to establish these averages, all deflections were measured and recorded to the nearest 0.1 mm.

The maximum and minimum deflections of the RS-T segments and T waves are also shown respectively above and below the figure representing the average of these measurements.

Both the maximum and minimum figures represent a single case in the series of fifty between the ages of 21 and 30 years, and in a series of twenty-five each in each succeeding decade.

Since the individual electrocardiogram must be interpreted on the basis of such maximum and minimum deflections, the presentation of this spread appears desirable.

Only a few persons more than 30 years of age were subjected to anoxemia prior to the completion of our first series (aged 21 to 30 years). From these few observations and on the assumption that as age advances there should be some limitation in the coronary bed, we expected to find that the response would differ perceptibly in the older subjects. This was incorrect, for the response in each of the four decades which we studied was practically identical, as shown by a comparison of Figs. 2, 3, and 4 with Fig. 1 and Tables II and III. Although Levy and others had made this assumption in formulating their criteria for the normal response, there has been no previous work on which an authoritative statement could be based. These anoxemia tests extended over a period of nineteen months. Most of the normal subjects of the 51 to 60 year group were subjected to the test eight months after the youngest group, and therefore at a period when we were most familiar with the technique of the procedure. Since the



been engaged in investigative medicine and is especially occupied with problems of aviation medicine. These men not only observed but submitted themselves to the tests and made valuable suggestions toward improving and safeguarding the procedure.

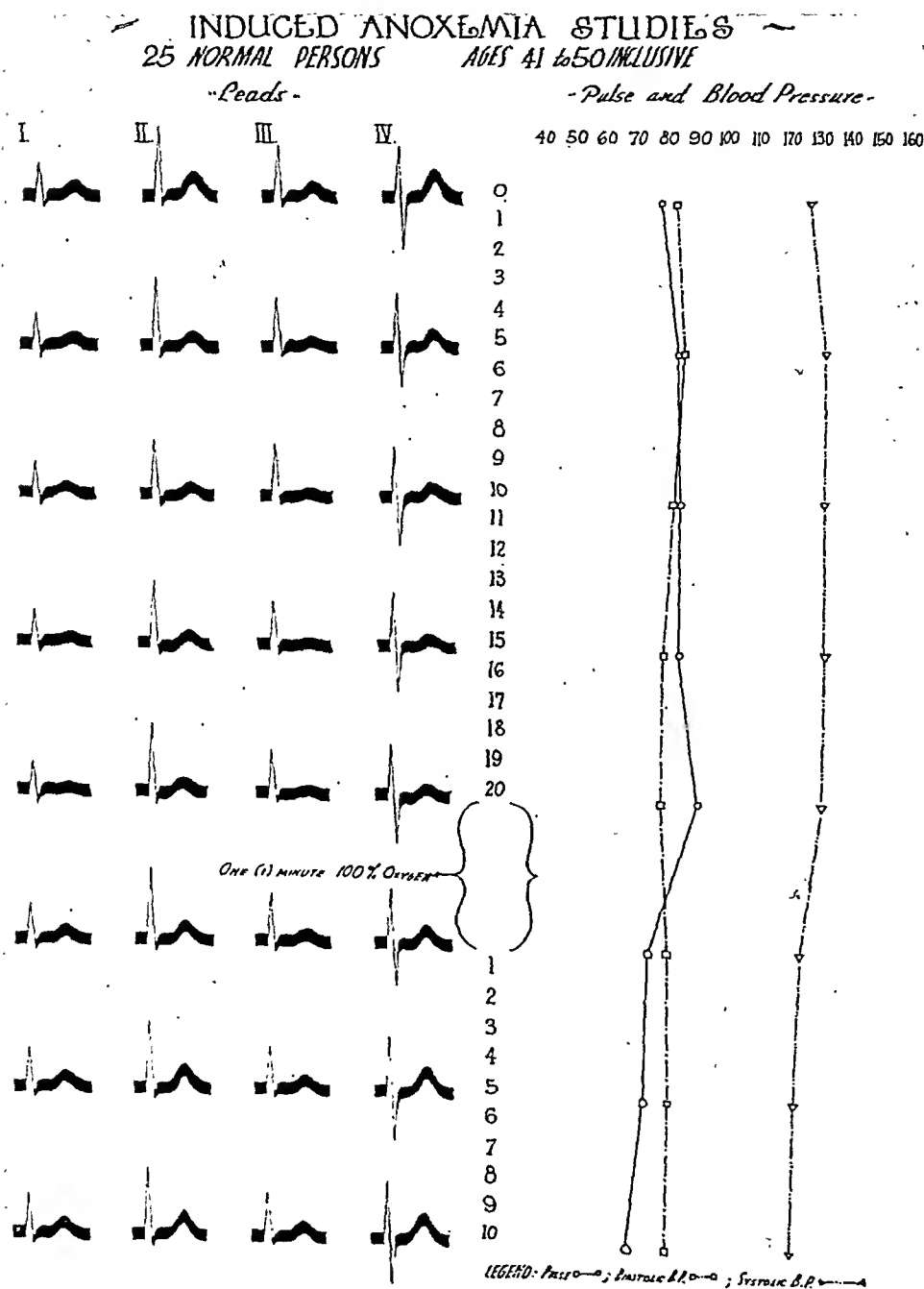


Fig. 3.

The pulse rate and blood pressure responses to anoxemia are shown in Figs. 1 to 4, inclusive. In the younger subjects (21 to 40 years), the



blood pressure changes in response to anoxemia. Our observations do not confirm those of Gellhorn<sup>19, 48</sup> and of Steiner, et al.,<sup>49</sup> who report elevation in blood pressure under anoxemia. We do not consider that the pulse rate and blood pressure changes described above have any clinical significance, but marked departure from this range of response may indicate an unfavorable and possibly dangerous reaction.

#### SUMMARY OF THE ELECTROCARDIOGRAPHIC OBSERVATIONS ON NORMAL SUBJECTS WHO SHOWED A "NORMAL" RESPONSE TO ANOXEMIA

There is an early and prompt depression of all T waves, especially T<sub>3</sub>, and, with this, a deviation of the RS-T segment from the isoelectric line; both become maximum at twenty minutes, and both return to the position observed in the control for that subject after the administration of pure oxygen, followed by air (see Tables II and III, and Figs. 1, 2, 3, and 4).

The foregoing is, in all essentials, in agreement with the criteria of Levy, et al.,<sup>4</sup> for the normal response to anoxemia, except the changes in Lead IVF, which will be discussed later.

We wish to present at this point, in summary,\* a group of cases in which there was no history or objective evidence of cardiovascular disease, including the control electrocardiogram, but in whom an "abnormal" response, according to the criteria of Levy,<sup>16</sup> was obtained.

#### LEVY'S CRITERIA OF AN ABNORMAL RESPONSE

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm. or more.
2. Partial or complete reversal in the direction of T in Lead I, if accompanied by RS-T deviation of 1 mm. or more in this lead.
3. Complete reversal in the direction of T in Lead IVF, regardless of RS-T deviation.
4. Partial reversal in the direction of T in Lead IVF, if accompanied by RS-T deviation of 1 mm. or more in this lead.

#### NORMAL SUBJECTS WHO SHOWED AN ABNORMAL RESPONSE TO ANOXEMIA

Some subjects showed what was, according to Levy, an abnormal response to induced anoxemia, but the history, absence of symptoms, and physical examinations failed to reveal any evidence of cardiovascular disease. In none of these was there any history of chest pain, congestive failure, or hypertension. In all cases the control electrocardiogram was normal in all four leads.

*Summary.*—Twenty-four of 125 normal persons (19.2 per cent) showed an abnormal response according to the criteria of Levy. Twenty-two of the twenty-four subjects showed complete reversal of T in Lead IVF (Levy Criterion 3); two of these also showed total RS-T deviations

\*The detailed protocols which were presented to the editor are omitted from this publication. Mimeographed copies of all case protocols will be furnished on request to the senior author.



of 3 mm. or more (Levy Criterion 1); and one showed complete reversal of  $T_1$  with RS-T deviation of 1 mm. (Levy Criterion 2). The age distribution of these is given in Table IV. When reversal of  $T_4$  occurred, it was observed that it was not always consistent. In several of the records it was noted that reversal was greater at fifteen than at twenty minutes.

TABLE IV

| TOTAL NO.<br>OF SUBJECTS | AGE<br>(YR.) | SUBJECTS WHO SHOWED<br>ABNORMAL RESPONSE |    | LEVY CRITERION<br>NO. |
|--------------------------|--------------|--|----|-----------------------|
|                          |              | NO.                                      | %  |                       |
| 50                       | 21 to 30     | 5  | 10 | 3                     |
| 25                       | 31 to 40     | 6  | 24 | 3                     |
| 25                       | 41 to 50     | 8  | 32 | 3                     |
| 25                       | 51 to 60     | 5  | 20 | 3                     |

It therefore appears that *reversal of T in Lead IVF (Criterion 3) in response to induced anoxemia cannot be accepted as indicative of coronary insufficiency.*

In two instances the control electrocardiogram suggested coronary disease, but there was no other confirmatory evidence. The response to anoxemia was "normal," according to Levy.

Five subjects were given 12 per cent oxygen and 88 per cent nitrogen at an early stage in this work and were therefore not included. Three of these complained of precordial pain, and we felt that one of them had probably had an old infarction. In the case of the other two we doubted the importance of this complaint. This particular gas mixture was used after one or two rather disquieting experiences, to be mentioned later, with the idea that a lesser degree of anoxemia might prevent undue strain and thus eliminate these effects. We found, however, that there appeared to be no significant difference between the response of these subjects and that of those who received the 10 per cent oxygen mixture, and, since we were attempting to set up normal standards for a clinical test, it seemed preferable to employ the same gas mixture throughout. The results of these tests were quite comparable to those in which the 10 per cent mixture was used, but are not included with them.

We present, in Table V, forty-five anoxemia observations which are not included in the series of 125 normal subjects. These appear in four groups. It will be noted that in twenty-four instances the test was interrupted. Since this usually occurred *after* definite evidence of profound anoxemia, especially in Group II, we believe that the inclusion of these results is warranted. In six instances we considered the results of no value because no significant anoxemic effect was produced. These are reported as "no record," and are included only in order to point out certain causes of failure in the anoxemia test.

There were nine cases in which there was a complaint of precordial pain of some type; in none of these had there ever been any objective evidence of cardiovascular abnormality. Of this group, *only two gave an abnormal response*, according to Levy's criteria, and one conformed

to all of the four criteria indicative of coronary insufficiency, but all other evidence in these cases was against this diagnosis.

In four of fifteen subjects who presented no acceptable evidence of cardiovascular disease, but, because of complaints, history of past disease, or confusing electrocardiograms, were not considered satisfactory for inclusion as normal subjects, we obtained a response which was abnormal, according to Levy. Since this study was primarily an attempt to set up normal standards, we avoided the intentional inclusion of persons who showed acceptable evidence of cardiovascular disease. However, seven persons who presented definite or equivocal evidence of a cardiac abnormality are presented in Group IV. Five of the seven showed an abnormal response (Levy). Of the seven, there were four in whom there was acceptable evidence of past coronary disease. Three gave an "abnormal" response. The patient who gave a "normal" electrocardiographic response (Case 30) was in such profound anoxemia that we felt impelled to interrupt the test at the end of fifteen minutes. This patient probably had had coronary occlusion about five years before the test, and certainly has coronary artery changes, yet the electrocardiographic response was comparable to that of normal persons. Levy<sup>37</sup> stressed that a positive test indicates coronary insufficiency, but that a negative test does not rule out that possibility, and explains<sup>16</sup> some of these negative (normal) responses as instances of "coronary spasm initiated by nervous reflexes." He stated that, in these cases, "the reduction in coronary reserve was not sufficiently great to be indicated by the test," or that the heart muscle lesions lie in "silent" areas with respect to the electrocardiogram.

Wood and Wolferth,<sup>38</sup> who studied conventional leads only, noted significant electrocardiographic changes in only about 50 per cent of the patients during anginal attacks. They stated: "The absence of EKG change during an attack of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur." A "normal" response to anoxemia in these cases in which there is acceptable evidence of a previous coronary occlusion may indicate adequate coronary anastomoses. That such anastomoses not infrequently occur in the arteriosclerotic heart was proved by Herrick<sup>46</sup> nearly thirty years ago, and by Gross,<sup>47</sup> in 1921, and has been more recently demonstrated by Schlesinger<sup>42</sup> and by Blumgart and his associates.<sup>41</sup>

Since the anoxemia test is designed to furnish objective evidence of coronary insufficiency, *a negative or "normal" response in a patient who presents equivocal evidence of coronary disease adds little to the diagnosis and may further cloud the clinical picture.*

We encountered a positive ("abnormal") response in two cases (Cases 8 and 128) in which satisfactory evidence of coronary insufficiency was lacking. In view of the fact that abnormal responses were obtained in some of our normal subjects, a diagnosis of coronary insufficiency does not appear justified in these cases.



### *Group II*

#### *Normal Subjects Showing Vasovagal and Cerebral Reactions*

[illegible]

*Group III*  
*Normal Subjects in Whom Test Was Interrupted Because of Development of Unfavorable Manifestations (Miscellaneous)*

[illegible]

*Group IV*  
*Persons Showing Some Evidence of Cardiovascular Abnormality*

[illegible]

N, Normal; Ab, abnormal; N.R., no record.

In a group of forty-five patients (not included in the normal series), with and without objective evidence of heart disease, there were sixteen who complained of pain which was sufficiently suggestive to warrant investigation, and they were subjected to anoxemia. Of these, nine complained of pain during the test, and in six, in our opinion, this was sufficiently severe to warrant interruption of the test.

In the three subjects who complained of pain or discomfort during anoxemia, but completed the test, one electrocardiographic response was normal and two were abnormal. Seven subjects had complained of pain but did not experience it during the test; the electrocardiographic (completed test) response was normal in one and abnormal in two, and, in the incomplete tests, normal in one and abnormal in one. No record was obtained in two of these cases. From this small group of cases it appears that, although pain may occur and interfere with the completion of this test, *the occurrence of pain during the test is not of much diagnostic value.*

Others<sup>4, 14, 16, 27</sup> have noted the variability of the occurrence of pain during anoxemia, but there appears to be no agreement as to the degree of anoxemia required to produce pain, and its bearing on the safety of the test.

Not one of the nine who complained of pain during the test showed evidence of cerebral anoxemia, as indicated by failure to respond to stimuli. It is possible that this might have been noted in some of the six tests which were interrupted because of pain.

Of the seven patients who had either a satisfactory history or signs of cardiovascular disease, three (Cases 30, 56, and 174) developed evidence of cerebral anoxemia which caused us to interrupt the test. Muscle twitching also occurred in Case 125, but, although the test was completed, we wonder, in retrospect, whether this was justified.

Evidence of cerebral anoxemia was a cause for the interruption of fifteen anoxemia tests. In nine there was failure to respond to visual or auditory stimuli. In five instances, muscle twitching, increasing to generalized convulsive movements, developed. In two instances convulsions occurred, at five and fifteen minutes, respectively, in subjects who had no evidence of cardiovascular disease. In each the convulsion was terminated by inhalation of oxygen. An interesting point in connection with these five cases is that, in spite of repeated responses to stimuli, these patients went into a convulsive state without premonitory manifestations.

Nearly twenty years ago, Haldane<sup>44</sup> warned that, when certain persons are subjected to anoxemia, there is little warning before actual unconsciousness occurs. Levy<sup>37</sup> reported two instances of convulsions during the test. It appears evident from even this limited number of cases that constant observation during the test for evidence of cerebral anoxemia, as indicated by failure to respond to stimuli, may not prevent the development of a sufficient degree of cerebral anoxemia to lead to con-

vulsions. Hartman<sup>20</sup> has called attention to residual changes in the brain after even short exposures to anoxemia; these changes consist of perirascular hemorrhage, edema, and vacuolation, with resulting degenerative changes in the substance of the brain. It would appear that this might possess potentialities which we would not wish to introduce as a side effect of a diagnostic procedure.

#### REGARDING HAZARDS INCIDENTAL TO THE ANOXEMIA TEST

Although the majority of the subjects completed the test without any symptoms which caused them or us any concern, we have encountered untoward symptoms in seventeen instances in a total of 189 tests. In all but two of these instances we felt impelled to interrupt the test. Of this total number of cases in which such manifestations occurred, five had symptoms of such severity as to furnish cause for alarm. We wish, therefore, to discuss at this point certain dangers which are incidental to this test even when it is carried out with the most meticulous care, for under no other conditions should any normal person be subjected to induced anoxemia, and this applies more forcibly to the subject with possible coronary insufficiency.

In a clinical experience of more than thirty years (C. T. B.) there have been numerous instances of acute heart strain associated with a change from sea level to Denver, and also with changes from the altitude of Denver to still higher altitudes. With more rapid means of transit, by streamlined trains which go from what is practically sea level to a mile-high elevation within seventeen hours (with 80 per cent of this ascent within less than nine hours), and by airplanes which cover the same distance within five and one-half hours, this hazard is of increasing importance. The hazards of air travel have been discussed previously.<sup>15, 27</sup> White<sup>23</sup> reported the death of a 27-year-old air corps pilot from coronary thrombosis very shortly after a flight which probably did not exceed 5,000 ft. in altitude. All previous history and examinations had indicated that he "was considered one of the better physical specimens in a group of highly selected and physically fit individuals." When he took off, he appeared to be perfectly well; on landing he was acutely ill and died within three hours. It was learned later that he had been taking sulfanilamide, which may have been a factor in the production of anoxemia, but it is certain that the cardiac accident occurred while he was in the air.

A 12 per cent oxygen mixture at Denver furnishes conditions equivalent to an altitude of 19,400 ft., and a 10 per cent mixture, to one of 23,500 ft. (at sea level, to 19,200 ft.). Either altitude is rarely attained in commercial air flights and never in this part of the world in travel by train, but in this test the subject is exposed very shortly after the beginning of the procedure, and for nearly twenty minutes, to the equivalent of an altitude of 19,200 to 23,500 ft. Both cardiovascular and cerebral disturbances have occurred in the course of induced

anoxemia tests. Levy, et al.,<sup>16, 27</sup> reported three instances of acute pulmonary edema, one of which developed after six minutes of 12 per cent oxygen (altitude, 16,000 ft.); in another, the patient was in shock after ten minutes of anoxemia (percentage of oxygen not stated). These two instances were encountered in men of 65 and 61 years, respectively. Acute pulmonary edema represents an extreme stage of failure. Minor evidence of failure is difficult to recognize early but, when once established, may progress to an extreme stage in a very short time. How many cardiac patients may experience slight degrees of failure induced by this test can only be conjectured at this time. We have been fortunate in that in none of our untoward results has failure been an apparent factor.

In a recent paper, Gross and Sternberg<sup>40</sup> pointed out that, in the course of certain functional disturbances, "circulatory disturbances severe enough to cause necrosis of the cardiac muscle" may occur, even in the absence of any demonstrable vascular lesion. As examples of such functional disturbances they cite "fall in aortic blood pressure as in peripheral shock, and phasic variations in the coronary flow"; and say that, in pathologic states, "the systolic coronary flow may provide the major nutrition of the heart." Blumgart, et al.,<sup>41</sup> stressed the "importance of avoiding fall in blood pressure from any cause in coronary arteriosclerosis." In certain instances we have noted a sudden and profound reduction of the blood pressure, which, though transient, might furnish the precipitating factor leading to infarction.

In animal experiments, partial to complete heart block has been produced by anoxemia.<sup>31, 33, 45</sup> Bundle branch block was described by Resnik,<sup>1</sup> who has observed bundle branch block and auricular and ventricular fibrillation during *experimental* anoxemia. We have not seen any of these conduction or rhythm disturbances, but the possibility of their occurrence during the test appears to present an incidental hazard.

Less dramatic than these instances of muscle or conduction system failure are certain vasovagal and cerebral manifestations which others<sup>27</sup> and we have observed. Reasoning from observations made in the course of aviation studies, and from the studies of Schneider and Lutz,<sup>18</sup> in 1920, Armstrong and Heim<sup>24</sup> stated that there are two general types of reactors to anoxemia, "fainters and nonfainters." They stated: "The fainters are those in whom the lower centers which control heart rate, vascular tone, and the rate and volume of breathing, suffer paralysis before the higher or psychic centers are affected. The non-fainters exhibit a failure of the psychic centers before the cardiac, vasomotor, and respiratory centers become seriously affected." They had noted sudden unconsciousness without any preceding evidence of abnormality. In our experience, fainting was not an uncommon occurrence. In a series of 132 normal persons, we noted a sudden fall in pulse rate and blood pressure, and pallor and/or syncope in seven cases. Table V presents in detail these signs and symptoms of vasovagal disturbance. Although none of these

proved to be at all serious, and cleared up immediately under oxygen administration, there is evidence of a profound involvement of the higher centers in these cases. Many of these vasovagal reactions occurred in psychoneurotic persons. McFarland<sup>25</sup> believed that this type of person is more susceptible to oxygen lack than normal subjects and that their cardiovascular reactions are subnormal. With both of these views we agree. He encountered fainting more frequently in the younger subjects. We have been surprised to note this and other vasovagal manifestations as frequently in the normal subject over 40 years of age as in our younger group of normal persons.

We have often had tests interrupted by the patient. Although this seems to be due to lack of cooperation, it may represent evidence of cerebral anoxemia, for mood and memory changes occur during generalized anoxemia.<sup>19</sup>

Vague symptoms suggesting coronary insufficiency frequently occur in the psychoneurotic person. Some objective evidence is especially desirable in these cases, but we have been obliged to interrupt the test, or it has been interrupted by the patient's removal of the mouthpiece, in about 50 per cent of the tests on subjects of this type. Since the time consumed in this test and the expense are factors, we consider the induced anoxemia test of doubtful value in this type of person.

Armstrong and Heim<sup>24</sup> stated that, at 14,000 ft. and above, "there is a progressive deterioration of voluntary muscular control," evidenced by "ineoordination of finer muscular movements—slowing of movements, tremor and final paralysis." Experimentally, in guinea pigs and cats, and with higher degrees of anoxia,<sup>22</sup> spasmodic movements varying from isolated clonic twitching to generalized convulsions have been observed. Most of these changes are probably reversible, but there is evidence, as pointed out below, that this may not always be the case. In five instances, muscular twitching occurred in the course of anoxemia and, in two of these, progressed to generalized convulsions before the anoxemia could be terminated by oxygen inhalation. This appears to us to present a real hazard, for it has been shown that functional, and even structural, changes may take place in brain tissue during even brief exposure to anoxemia.<sup>22</sup>

That the brain is especially vulnerable to oxygen lack has been amply demonstrated in the course of recent studies, especially those concerned with the shock therapy of schizophrenia.<sup>26, 32</sup> Experimentally it has been shown that under anoxia both parasympathetic and sympathetic centers are excited to a varying degree and that mood and memory changes develop under 8.5 per cent oxygen.<sup>19</sup> Hartman<sup>20</sup> has shown that, in the anoxemia associated with shock, sedation, and fever therapy, perivascular hemorrhage, pericellular edema, vacuolation, and degeneration occur.

It is true that the time element in this type of therapy differs from that in the test under discussion, and that it is not customary to



subject anyone to anoxemia a second time within a twenty-four-hour period; this point has been stressed by Levy.<sup>16</sup> But even with slight anoxia (degree not given), Hartman<sup>21</sup> stated that one may encounter later neural lesions. Experience with aviators who have subjected themselves to repeated exposure to low oxygen tension suggests the possibility that a lowered cerebral reserve may account for the fact that, as their air experience increases, their ability to fly at high altitudes (without oxygen) diminishes.<sup>22</sup>

At oxygen partial pressures equivalent to an altitude of 28,000 ft. it is stated that cortical changes occur.<sup>22</sup> Some of these changes may become permanent. This is a lower oxygen pressure than that usually and intentionally employed in this test but not lower than that employed by mistake in six of our tests. We have mentioned an error (manufacturer's) in the oxygen percentage which occurred at an early stage in the work. Six persons were subjected to a mixture containing 8.6 per cent oxygen (equivalent to an altitude of 31,000 ft. approx.) before the error was discovered. Since that time the contents of each tank have been analyzed before use and re-examined if there was any cause for question. All of these subjects showed evidence of extreme anoxemia. In two instances the test was interrupted at three minutes (Case 42) and at twelve minutes (Case 43), respectively, because of suffocation. One subject (Case 41) had slight blurring of vision and headache at twenty minutes, and one (Case 40) at nineteen minutes failed to respond to stimuli and had a generalized tremor; but in both cases the electrocardiographic response for the completed test over a twenty-minute period of such high-grade anoxemia was normal. The four above-mentioned subjects were "normals" between the ages of 21 and 30 years. Preceding the four tests just mentioned, we had subjected two older men to this test. Case 38 (aged 45 years), who was normal on physical and electrocardiographic examination, was born and lived for seventeen years at an elevation of 9,577 ft.; since that time he has lived mainly at this mile-high elevation and is accustomed to mountain activities. He reported a sensation of plugging in the ears which was comparable to what he had noticed on several occasions when he was exposed to reduced barometric pressures. He stated that he experienced some discomfort during the test and felt definitely shaky after it. He had a throbbing headache which lasted all evening and even some "hangover" the next morning. His completed test showed an abnormal response, according to Levy's Criterion 1, and was questionable with respect to Criteria 2 and 4. Case 39 (aged 47 years) has resided in Denver for fifteen years. We learned later that he had some hypertension, without other evidence of cardiovascular abnormality. He reported that he felt as if he were close to the initial stages of anesthesia toward the end of the test. He was also quite uncomfortable and had some headache afterward and some "hangover" the next day. His completed test showed an abnormal response according to all four

of Levy's criteria. These two men are experienced physiologists whose observations we consider dependable. Consistent with their observations are those of McFarland,<sup>25</sup> who stated: "In the subjects who collapsed, the headaches, nausea, palpitation, pain in the chest and muscular twitchings lasted from one to ten hours. Even in several of the subjects who reacted easily, some of the after-effects mentioned above were noticeable for one to two hours later."

These experiences were so impressive that we took care to ensure accuracy in our gas percentages. It is a matter of interest that but one of the six men who were subjected to this extreme grade of anoxemia showed muscular tremor, and none had convulsive movements, although four were carried through twenty minutes of anoxemia, which is equivalent to an altitude of 31,000 ft. (approx.). These observations are in accord with those of Michelson and Thompson,<sup>28</sup> who found that the degree of anoxemia does not bear a quantitative relationship to the severity of the clinical manifestations, for, under identical conditions, the arterial oxygen saturation may vary in different persons. But that such a degree of anoxemia may produce distinct morphologic changes appears to be proved. In the individual case there seems to be no means of predicting whether such damaged cells can recover.

There are certain physiologic responses which tend to offset the unfavorable cardiac and cerebral responses above mentioned. McFarland<sup>25</sup> quoted a French investigation in which it was found that the carotid body is especially sensitive to anoxemia and that, when so stimulated by a relative excess of carbon dioxide, there is a compensatory increase in circulation and respiration; "thus more oxygen is supplied to the deficiency of the respiratory, cardiac and vasomotor centers." Wiggers<sup>34</sup> stated that, contrary to data in the literature, anoxemia has a stimulating effect on the heart and that the economy of the ventricle is improved under such degrees of anoxemia as are being discussed here. If this is correct, it would seem that evidence of cerebral and myocardial ischemia should never occur under conditions of anoxemia.

#### DISCUSSION

We have presented the results of a series of observations on 125 persons who were entirely normal from the cardiovascular standpoint and were subjected to anoxemia induced by the inhalation of a 10 per cent oxygen mixture. These studies lead us to believe that there is a usual, or "normal," response, consisting of practically no symptoms, but of certain rather definite changes in the electrocardiographic pattern which are promptly reversed by the inhalation of oxygen. These changes have been presented clearly in tables and charts. In spite of the generally accepted view that some physiologic change occurs in the coronary vessels in the later decades, we found no significant difference in the electrocardiographic responses which take place in persons 50 to 60

years of age, as compared to the three preceding decades. We have described a usual, or "normal," response. However, in a significantly large group (19.2 per cent) of subjects whose history, physical and electrocardiographic examination, and response to exercise were normal, who were, in fact, by every usual clinical standard, considered normal, we found an electrocardiographic response which has been described by Levy<sup>4, 16</sup> as indicative of coronary artery insufficiency. We believed that Levy had demonstrated the value of this procedure in clinical diagnosis, although, as stated before, we were dissatisfied with the basis for his normal criteria. As this work progressed we reluctantly came to the conclusion that a test which gave an "abnormal" response in 19.2 per cent of normal persons, and as frequently in the younger age groups as in the last decade studied, would be of doubtful clinical value. After eighteen months of experience we have had frequent failures due to technical error or lack of cooperation on the part of the subject. Unpleasant or even alarming symptoms occurred in sixteen instances. That there is some correlation between the efficiency of the coronary circulation and the electrocardiographic response seems apparent, but we have encountered "abnormal" responses in normal subjects and "normal" responses in abnormal subjects too frequently to justify, in our opinion, the use of this test as it is at present employed in clinical diagnosis.

If there is a difference between the responses of persons living at sea level and those residing in Denver, we wish to point out that a smaller number of normal persons should show an "abnormal" response at the high altitude than at sea level, for this group has been acclimated to low oxygen tension.

This work may be criticized because of the actual oxygen want to which the subjects were exposed, due to the lower partial pressure of our atmosphere. We exposed our subjects to greater anoxic strain than Levy did at sea level, but this strain was not as great as the difference in partial pressure would indicate. This, we believe, is compensated partially by residence in this altitude, but, if this is not the case, it would seem that our group of cardiovascular patients should have shown a more unfavorable and more consistently abnormal response than they did.

The accepted idea that some degree of coronary artery change is associated with the aging process is not supported by these studies. This means either that the induced anoxemia test is not a dependable means of demonstrating coronary artery disease, or that such disease does not consistently occur in the later decades. We favor the former opinion.

In 1928, Keefer and Resnik<sup>5</sup> wrote: "Unfortunately there is not at present an absolute criterion of the diagnosis of angina pectoris—the decision in an individual case must be determined by the outcome." In the utilization of induced anoxemia it has been thought that we may

very well be approaching that "absolute criterion." The results of our investigation appear to leave us in the same position as that of Keefer and Resnik, in 1928.

#### CONCLUSIONS

1. The data which have been presented describe the "normal range" of electrocardiographic response to induced anoxemia in clinically normal subjects.

2. These electrocardiographic changes progress with the continuation of anoxemia but are promptly reversed by the inhalation of 100 per cent oxygen.

3. There was practically no difference in this response in the various age groups studied.

4. A different response was encountered in 19.2 per cent of clinically normal persons. This response has been described elsewhere as indicative of coronary artery insufficiency. We are not in accord with this idea.

5. Induced anoxemia cannot at the present time be considered a routine laboratory procedure which is devoid of all danger to the patient and free from the possibility of misinterpretation of electrocardiographic changes.

6. We feel that a word of warning is in order regarding the application of this test in clinical investigation. Meticulous care in the selection of the subjects, and especially in the performance of the test itself, will prevent some of the unpleasant experiences noted by others and ourselves. To this end, teamwork is essential. For the present the test should be considered as strictly a hospital procedure.

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## DISCUSSION

DR. DAVID MILLER, New York, N. Y.—Dr. Burnett's excellent studies raise a question—and I wonder whether he has any comment on this question—whether, in subjecting a normal heart to low oxygen tension, one may not be dealing fundamentally with the effect of deprivation of oxygen on central autonomic nuclear masses, rather than on the heart, or perhaps both. The responses which Dr. Burnett elicited seem to indicate that, with this low oxygen tension, the upper level of the brain and the brain stem are particularly concerned with the autonomic control of the cardiovascular apparatus. It is now known to physiologists that different levels of the brain stem and cortex react best at certain different, and specific, oxygen concentrations.

However, without laboring the point, it seems to me that in this kind of test the normal subject may be reacting primarily by virtue of some change in his heart muscle, or that the cardiac effect may be only a localized expression of a much more extensive autonomic effect. If we, as clinicians, are to employ a test of this character, we must be certain that the effect is chiefly and primarily on the heart and not widespread and generalized.

The second point I want to talk about is the matter of syncope in association with cardiovascular states. It is a commonplace that, when there is cardiovascular depression, syncope is very likely to occur, but syncope may also occur without cardiovascular depression. Stimulation of the *labium cerebri* will produce very marked signs of cardiovascular depression but no syncope. On the other hand, stimulation of the trigon zone has often produced a marked change in the cardiovascular apparatus. It is possible to produce cardiovascular changes, without syncope, by stimulation of higher areas in the cerebrospinal system.

It seems to me that this raises an important point. It is practical for us to consider whether there may not be a separate mechanism which is responsible for syncope, just as the effects of impulses from the periphery of the body which lead

into the neuraxis are referred to as cardiovascular changes. Is it not possible that syncope is the result of stimulation of specific areas of the neuraxis? If so, the mechanism is distinct from others.

DR. DOUGLAS DEEDS, Denver.—Dr. Burnett and his co-workers are my colleagues at the University of Colorado School of Medicine, and I am happy to have this opportunity of congratulating them on the tremendous amount of work they have done on this subject.

I have been doing Levy tests on my private patients at our mile-high altitude, also. I have not encountered any untoward reactions even in bona fide abnormalities, and do not consider the test dangerous.

To aid in acquiring a better understanding of my results, tests were done on myself at sea level by Dr. Levy, with a 10 per cent oxygen mixture, and later the process was repeated at mile-high altitudes with the same 10 per cent oxygen mixture. Objectively there was no significant difference, but subjectively the difference was considerable. Because of my studies I should like to suggest that, before we conclude that the Levy test is an unsatisfactory and dangerous test at our altitude, we must run another series of tests, using a 12 per cent instead of a 10 per cent mixture, to see whether the same untoward reactions and T-wave inversions occur.

I say this because, in discussing this matter with competent authorities, I am told that the oxygen saturation of hemoglobin (which varies greatly with changes in atmospheric pressure) is the important feature and that a person who lives at our altitude is not able to compensate completely for the difference in atmospheric pressure, regardless of his length of residence.

In Denver we are exactly one mile above sea level and have an average atmospheric pressure of 627 mm. of mercury; at sea level the latter averages 760 mm. For practical purposes this means that, gasometrically, 10 per cent of oxygen at sea level is equivalent to 12 per cent of oxygen one mile above sea level. Similarly, 8 per cent of oxygen in New York City is about equivalent to 10 per cent in Denver.

In my opinion, if Dr. Levy's normal standards, established in New York, are to be applied at our altitude, we should use 12 per cent and not 10 per cent oxygen mixtures. If Dr. Levy had used 8 per cent oxygen mixtures in establishing his standards, he, too, might have encountered the high incidence of untoward reactions and T-wave inversions in Lead IVF which have just been described by Dr. Burnett.

Certainly, we need some method of diagnosis which is more accurate and helpful than our clinical opinion, plus the resting electrocardiograms, in diagnosing preocclusive coronary sclerosis. Despite its disadvantages, to date, the Levy test has answered this real need better than any previous diagnostic adjunct. Although I shall retain the open mindedness which I have always had regarding such diagnostic aids, I plan to continue my use and scrutiny of the Levy test, for only by the continuation of such studies will we lessen a serious diagnostic weakness.

DR. LOUIS N. KATZ, Chicago.—Considering the potential hazards of anoxemia, which we also noted several years ago, I feel strongly that patients with suspected coronary disease should not be subjected to this test routinely.

DR. CLOUGH T. BURNETT.—In a letter to me Dr. Levy raised the question whether our records were not vitiated by an experience similar to one I mentioned at the meeting of this Society last year in connection with the discussion of his paper, namely, an error in the percentage of our oxygen. This will be discussed when our paper is published, but was not mentioned in that portion just presented. Six persons, through the manufacturer's error, were consecutively subjected to an 8.6 per cent oxygen mixture before the error was recognized. I can assure those here,

and assure Dr. Levy, that that error occurred in only six instances, but it was not until the sixth that we realized that something was wrong. Since then, repeated gas tank analyses have prevented further errors of this sort.

Dr. Levy raises a question, as does Dr. Deeds, as to the elevation at which we are working. Theoretically, we did place these subjects under a greater strain than does Dr. Levy, but we maintain that one who has resided at a mile-high elevation for at least several months—and many of our subjects have lived there for years—has become acclimatized to low oxygen pressure, and that fact should be taken into account.

Dr. Deeds has mentioned the difference in the response to the test as done in New York and as done in Denver. Dr. Nims, one of my collaborators, had a test run in Dr. Levy's laboratory, as well as one in Denver, and he did not notice any difference. I have never been tested at sea level. I was tested in Denver and was one of the easy and normal reactors. Personally, I should just as soon do it again tomorrow, because I know how I reacted. The difficulty is that we cannot predict which subject will have syncope, which will develop vasovagal reactions, and which will have convulsions. Until we can work out some means whereby that can be satisfactorily known, I believe there is a hazard which prevents the ready acceptance of this test in clinical diagnosis.

Dr. Miller has discussed the autonomic responses. These occurred unpredictably. Age did not seem to make any difference. When we finally completed our work, we did not feel that, with the initiation of any test, we could tell whether we were going to be able to complete it or not. We should be open minded, but I believe that, when a team which worked as long as we worked on this investigation continued to encounter the difficulties we did, and when, in addition, the interpretation of the response is subject to a considerable element of error, the test is of doubtful value in clinical diagnosis.



A METHOD FOR PERFUSION OF RABBITS' EARS, AND ITS  
APPLICATION TO STUDY OF THE RENIN-ANGIOTONIN  
VASOPRESSOR SYSTEM, WITH A NOTE ON  
ANGIOTONIN TACHYPHYLAXIS

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**S**TUDY of the renin-angiotonin vasopressor system has been facilitated by a method with which isolated organs can be perfused with both blood and Ringer's solution, employing a pulsatile pressure. For most investigations, the rabbit's ear has proved to be the organ of choice. The purpose of this communication is to describe this method in detail, so that it can be reproduced when sufficient dexterity is achieved.

It may interest the reader if the field to which the method has been applied is briefly outlined. Purified renin exhibits no vasoconstrictor properties when it is perfused through a rabbit's ear in Ringer's solution,<sup>1</sup> but, when a fraction of the pseudoglobulin (tentatively called renin-activator)<sup>2, 3</sup> of the blood is added, interaction occurs, and a third substance is formed which causes vasoconstriction. A thermostable substance was isolated, crystallized, and termed angiotonin.<sup>4, 5</sup> But angiotonin itself is probably unable to act in a rabbit's ear perfused with Ringer's solution in the absence of a substance in the plasma which has been called angiotonin-activator.<sup>6</sup>

Kidneys in which the pulse pressure has been reduced liberate renin.<sup>7, 8</sup> It is our belief that this renin combines with renin-activator to produce angiotonin. In the renal veins, therefore, a mixture of renin and angiotonin may be found,<sup>9</sup> but in peripheral blood an "angiotonin-like" substance occurs.<sup>10</sup> The latter is detected by injecting plasma from a hypertensive dog into blood, being perfused through a rabbit's ear, from a dog in which both kidneys have been removed ("arenal" blood). This substance is much increased in animals with experimental hypertension, in patients with essential and nephritic hypertension, and in normal dogs and rabbits after the injection of renin. A somewhat similar line of reasoning has been developed by Munoz, Braun-Menendez, Faseiolo, and Leloir.<sup>11</sup>

*Method for Perfusion With Pulsatile Pressure.*—Two types of apparatus have been designed and built, chiefly by Mr. Clifford Wilson, of the Lilly Laboratory for Clinical Research, for perfusion of organs. The first type is simpler to construct but does not offer the flexibility of adjustment inherent in the second. Both types have proved very satisfactory in practice for four years.

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Pulsation is imparted to the air jet in the first type by means of a "windshield wiper" respirator, and, in the second, by a motor-driven cutoff valve.\* The systolic

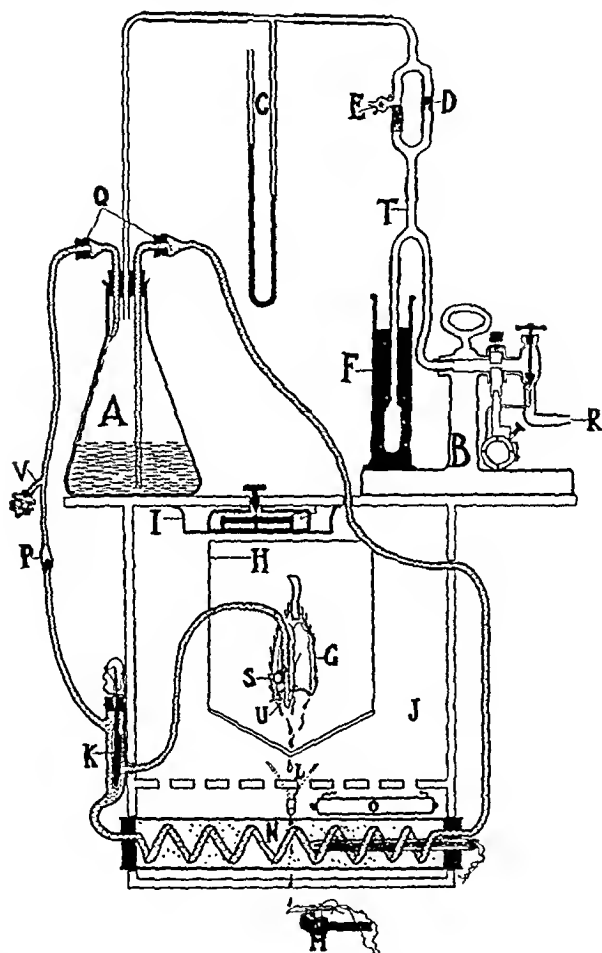


Fig. 1.—Pulsatile Pressure Apparatus. A, Ringer-Locke's solution reservoir (1,000 c.c.), fitted with a three-hole rubber stopper, through which pass three glass tubes (air pressure, fluid delivery, and fluid return tubes); B, artificial respirator ("windshield wiper" type) to furnish pulse; C, mercury manometer; D, one-way air valve; E, pressure relief valve (when properly set, will allow air to escape from the system after each pulse, to give desired diastolic pressure); F, peripheral resistance (made by submerging a fast-filtering Berkefeld filter in mercury to a depth necessary to prevent the escape of air up to desired pressure, and to exhaust all air in excess; this pressure is the systolic); G, rabbit's ear; H, glass plate supported at 45° angle, upon which the ear is placed; I, thermoregulated incubator; J, thermostat for incubator; K, thermometer; L, drop recorder to measure flow through ear during perfusion; M, heater consisting of these the glass eoll carrying solution and heater are fitted; N, heater for incubator; O, one-way return cone valve to protect ear from back pressure when exchanging or circulating perfusate with the aid of a syringe connected at P; Q, one-way flap valves connected to the fluid delivery and fluid return tubes; R, air inlet (to be connected to constant-pressure air line); S, side arm fitted with serum bottle stopper, through which injections are made into the ear that has been cannulated; T, pulsating air jet; U, glass cannula inserted into the artery of the ear; V, T-tube for exchanging or circulating perfusate.

and diastolic pressure is regulated by a submerged Berkefeld filter in the first type, and by a rubber "peripheral resistance" in the second. Injections into the stream of fluid perfusing the ear are made through a serum bottle stopper, which is inserted into a side arm directly above the arterial cannula. The glass plate on which

\*Arthur H. Thomas and Company—Respiration cutoff valve, catalogue No. 8107

the ear rests is grooved so that all fluid issuing from the cut ends of the veins will run immediately into the collecting funnel and be recorded. It was found that the Ringer's solution, dropping on the electrical contact points, soon corroded them; hence, a flask filled with 500 c.c. distilled water, with a side arm from which the diluted fluid dropped onto a recorder, was inserted. The tipping-spoon type of recorder was found to be even more satisfactory. Accurate temperature control was achieved by thermostats in both the box housing the ear and the water baths containing the Ringer's solution reservoir. If blood is used as the perfusion medium, a Baxter wire-gauze filter, as used in transfusion sets, is inserted into the line delivering the perfusate to the ear. Not shown in either figure is a humidifier in the box containing the ear. It consists of a pan of water, covered with wire gauze on which surgical gauze is spread.

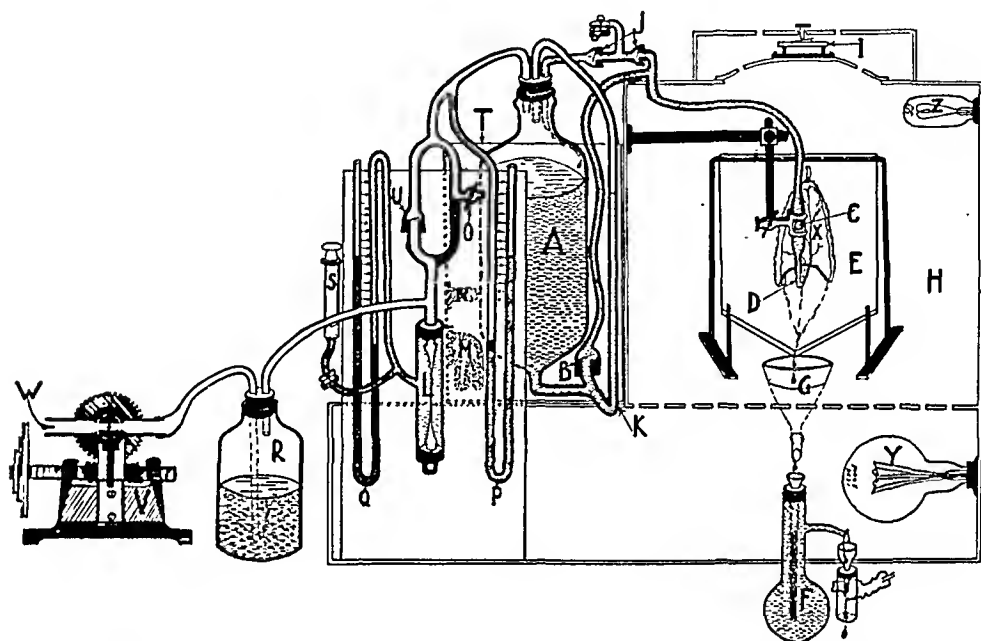


Fig. 2.—Pulsatile Pressure Apparatus. *A*, Reservoir for Ringer-Locke's solution; *B*, one-way valve; *C*, serum-bottle stopper fitted on side arm (through which injections are made); *D*, glass cannula (which is inserted into the artery at the base of an excised rabbit's ear); *E*, glass plate (supported on stand at 45° angle); *F*, flow recorder; *G*, glass funnel (to catch liquid flowing from ear); *H*, incubator (in which the temperature is regulated); *I*, incubator thermostat; *J*, one-way valves; *K*, reservoir gauge; *L*, peripheral resistance (this is made by stretching a thin elastic rubber tube through a cylinder; the pressure within this cylinder may be adjusted to any desired level); *M*, water-bath heater; *N*, water-bath thermostat; *O*, pressure relief valve (releases air in system in amounts necessary to establish desired diastolic pressure); *P*, manometer (records systolic and diastolic pressure in perfusion system); *Q*, manometer (records pressure exerted by peripheral resistance *L*); *R*, air-washing bottle; *S*, syringe (enables one to regulate the pressure exerted by liquid against rubber tubing in *L*, which is water cushioned); *T*, water bath (in which the temperature is regulated); *U*, one-way valve (through this valve air passes to the perfusion system; the amount of air passing to the system to build up pressure within it cannot exceed that of the peripheral resistance, thus establishing the systolic pressure); *V*, motor-driven cutoff valve (through which air blasts pass at regular intervals); *W*, air inlet; *X*, rabbit's ear (taped on glass plate); *Y*, incubator heater; *Z*, observation light (for ear compartment).

*Construction of Valves.*—Three different types of valves have been used in the construction of the perfusion apparatus.

1. *Flap Valve* (Fig. 3).—The construction of this valve is obvious from the drawing. The flap is made of rubber sheeting and is kept in place by a tiny bit of rubber cement on the edge. This valve facilitates thorough washing of the apparatus. It may be used with solutions which will corrode metals.

2. *Cone Valve* (Fig. 4).—A glass tube is heated at *D* until it melts sufficiently to thicken its wall. It is then pulled into a cone. Valve *C* is made from a glass

tube whose outside diameter will allow free movement within tube *B*. It is heated, pulled into a cone, and sealed with a heavy bead. The beaded tip is dipped into oil and emery, inserted into tube *B*, and ground until the joint fits smoothly. The valve is removed. All excess glass is cut off as close to the ground surface as possible. The valve is sealed, returned to chamber *B*, heated at point *A*, pulled out, and twisted into a spiral.

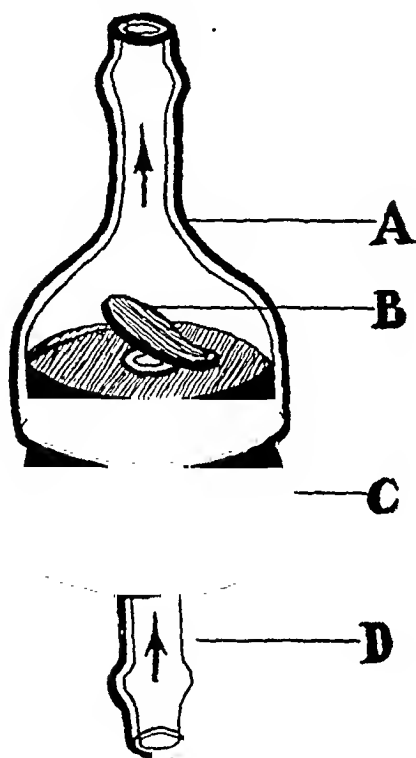


Fig. 3.

Fig. 3.—Flap valve.

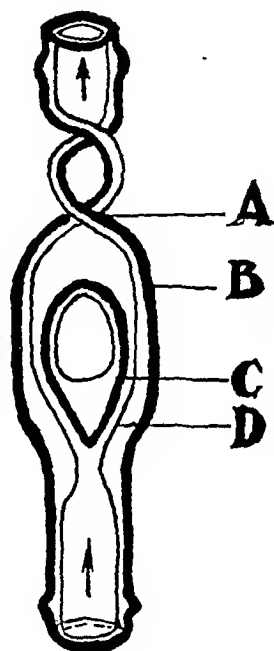


Fig. 4.

Fig. 4.—Cone valve. *A*, Chamber outlet; *B*, valve chamber; *C*, valve; *D*, valve seat.

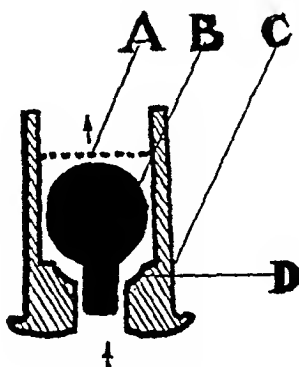


Fig. 5.—Air valve. *A*, Wire gauze; *B*, rubber or metal ball valve; *C*, cylinder containing valve seat *D*.

*3. Air Valve* (Fig. 5).—This type of valve is used only for air.

*Preparation of Perfusing Media and Samples of Blood for Assay.*—The renin employed was prepared by the method of Helmer and Page.<sup>12</sup> It was filtered shortly before use, for small particles of precipitate clog up the vessels of the

ear, thus simulating vasoconstriction. It was also necessary to dialyze it carefully, as undialyzed renin causes vasoconstriction. When perfused, it should cause no vasoconstriction.

Plasma was prepared for testing by drawing venous or arterial blood under oil into a syringe moistened with a solution of 50 mg. of heparin in 5 c.c. of isotonic saline, centrifuging, filtering the plasma, and storing at 10° C. Before being used, it was warmed to 37° C. and filtered through No. 42 Whatman filter paper. It was found that plasma could be kept for forty-eight hours, and perhaps longer, without losing its ability to activate renin. For the estimation of renin-activator, eight parts of plasma were mixed with one part of renin and allowed to stand at room temperature for ten minutes. The mixture (0.2 c.c.) was injected into the Ringer's solution perfusing the ear. Angiotonin-activator was estimated by first injecting small quantities of angiotonin until the vessels of the ear no longer responded by constriction. Plasma, usually 0.2 c.c., was then mixed with the standard dose of angiotonin and the mixture immediately injected.

Hemolyzed erythrocytes were prepared by first washing a weighed amount of cells with salt solution, hemolyzing with distilled water, bringing to isotonicity with salt, centrifuging, and filtering the supernatant fluid.

Tests were made on a fresh ear only when the drop rate was satisfactory (60 to 125 drops per minute with Ringer-Locke's solution) and were repeated when the original drop rate had been restored for at least five minutes. The whole experiment was usually finished within an hour and a half, for the ear tended to become edematous after this period. The amount of vasoconstriction was recorded both in terms of the length of time, in minutes and fractions thereof, which was required for the drop rate to return to its initial value, and the percentage reduction of drop rate. The percentage reduction was calculated by comparing the number of drops counted with a blood-cell counter during the period of vasoconstriction with the number during the period before the injection.

When blood was used as the perfusing medium, it was drawn from large dogs (18 kg.) from which both kidneys had been removed aseptically under pentobarbital sodium anesthesia (30 mg./kg.) twenty-four hours before. This so-called "areal blood" was sometimes heparinized (88 units per 65 c.c.) and immediately diluted in the proportion of 1:3 with Ringer's solution. If it was necessary to allow it to stand before use, it was put in an incubator at 37° C. and, before use, was filtered through washed cotton gauze. Usually the areal blood was defibrinated by shaking for seven minutes in a flask containing four spirals of copper wire which were prepared by winding the wire around pencils.

If the perfusion fluid to be employed was Ringer-Locke's solution, it was made fresh each day, as follows:

|                    |          |
|--------------------|----------|
| NaCl               | 9.00 Gm. |
| KCl                | 0.41 Gm. |
| CaCl <sub>2</sub>  | 0.24 Gm. |
| MgCl <sub>2</sub>  | 0.06 Gm. |
| NaHCO <sub>3</sub> | 0.50 Gm. |
| Dextrose           | 0.50 Gm. |

Make up to 1 liter with distilled water, and add sodium bicarbonate and dextrose last. Filter before use.

*Preparation of Ear.*—The ear of a young rabbit was found most suitable for perfusion. It was sponged at the base with water at 50° C., and then with one swift cut was severed from the unanesthetized animal by means of a sharp scalpel (Fig. 6). It has been found that the rabbit bleeds less and recovers more rapidly from amputation of the ear if no attempt is made to tie off the

vessels. A tie or hemostat will be scratched off as soon as the rabbit is free. Incisions were made on both sides of the artery, and a small hemostat was placed in such a way as to grasp the cut end of the artery and keep it free. A small

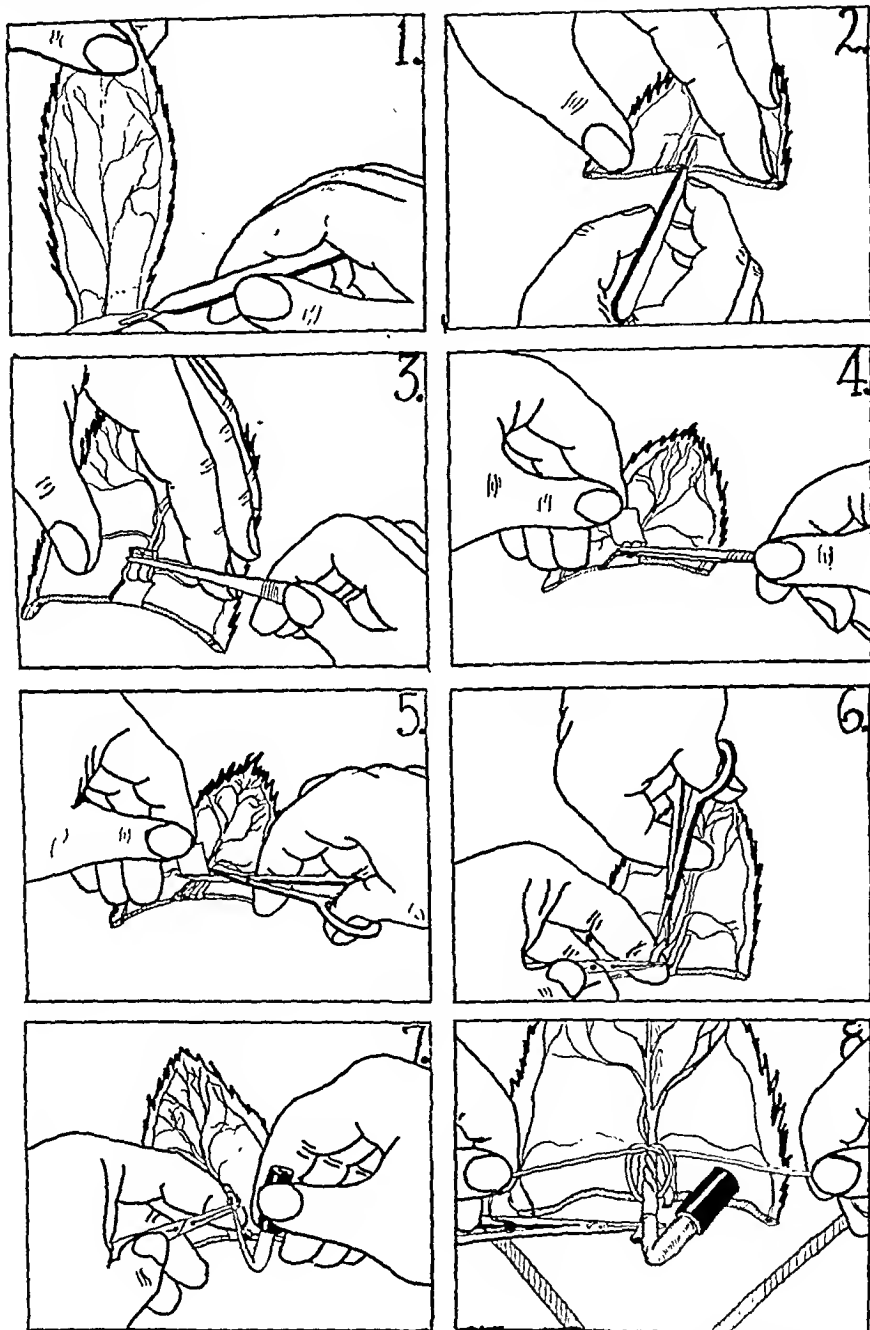


Fig. 6.—1. Severance of the ear with sharp scalpel. 2 and 3, Dissection of artery and vein. 4 and 5, Separation of vessels from skin flap. 6, 7, and 8, Insertion of cannula. These operations must be performed quickly and gently. There must be no tension on the cannula, and the artery should not project beyond the cut edge of the ear, lest drying of the vessel occur.

incision was made in the artery, and a glass cannula was quickly inserted and tied with silk; care was taken to traumatize the intima as little as possible. Warm Ringer's solution was used to wash out the remaining blood and insure

the patency of the cut ends of the veins. The tissues separated from the artery were then cut away. This entire operation should not take more than two minutes. *Gentleness and speed are vital to the success of the preparation.*

The ear was then placed on the draining plate and secured with adhesive tape, and a piece of string was placed against the cut surface to lead the perfusate into the collecting funnel. The cannula was connected to the apparatus with rubber tubing, and the warm (37° C.) perfusion solution was allowed to flow through the ear under the desired pressure (20/10-30/20 mm. Hg for Ringer-Locke's to 60/40-80/60 mm. Hg for diluted blood). The position of the ear must be correct, i.e., the artery straight, but not tense or twisted, and the system free of air bubbles. Perfusion proceeded more satisfactorily if the ear was undisturbed for a period of fifteen to twenty minutes. The beginning drop rate was very slow (four or five per minute) but gradually increased until a rate of 90 to 120 drops per minute with Ringer-Locke's solution had been reached. The ear was then ready for use. The drop rate should remain nearly constant throughout the experiment.

The ear to be perfused with blood was first washed through with Ringer-Locke's solution for a period of twenty to forty minutes, and then diluted blood was substituted. The average drop rate with blood was 16 drops per minute.

The usefulness of the ear was usually terminated by the occurrence of edema. The addition of acacia (20 c.c. of 6 per cent solution) to the Ringer's solution perfusing the ear occasionally seemed to reduce the rate of edema formation. Doubling the concentration, however, did not further decrease it. Experience has shown that the increase in weight of a satisfactory ear preparation was not greater than 8 Gm. in two to three hours.

It has proved wise always to perfuse a sample of the filtered plasma alone, before the addition of renin, to ascertain whether it, of itself, causes vasoconstriction.

If the blood had hemolyzed, vasoconstriction occurred when 0.2 c.c. of plasma was injected, whereas the same amount of plasma without hemolysis caused no vasoconstriction. Ears occasionally were so sensitive that they responded with moderate vasoconstriction to plasma alone. Such preparations were discarded. It was important to filter the plasma, especially when it had stood overnight, before injecting it into the ear. Particles of coagulated plasma form and clog the small vessels, giving the impression that vasoconstriction has occurred. The drop rate in such cases did not return to its initial value after the injection.

#### ACTION OF PITRESSIN, METHYL GUANIDINE SULFATE, AND TYRAMINE

Perfusion with pitressin (0.1 c.c. of 1:200 dilution) caused definite vasoconstriction which might be reproduced many times without marked loss of vigor. The addition of plasma from either hypertensive or normal dogs did not enhance its action. Methyl guanidine sulfate (0.2 c.c. of 1:200 dilution) also produced definite vasoconstriction which was not enhanced by the addition of plasma. From twelve to twenty injections might be given without significant decrease in response. Doubling the amount of methyl guanidine did not produce twice as much vasoconstriction. Tyramine (0.2 c.c. of 1:2,000 dilution) was about ten times as active as the same amount of methyl guanidine sulfate. Its action was unaffected by the addition of plasma. None of these substances proved suitable as standards for renin and angiotonin.

OBSERVATIONS ON THE ACTION OF RENIN-PLASMA MIXTURES AND  
ANGIOTONIN

The first injection often produced less vasoconstriction than did subsequent injections. When Ringer's solution was employed for perfusing the ear, as many as twenty injections might be given without loss of vigor of the response. When blood was employed, usually ten to fifteen injections might be made without any change in the sensitivity of the ear. It was noticed that renin-plasma mixtures did not cause edema of the ear as rapidly as did the usual vasoconstrictor drugs.

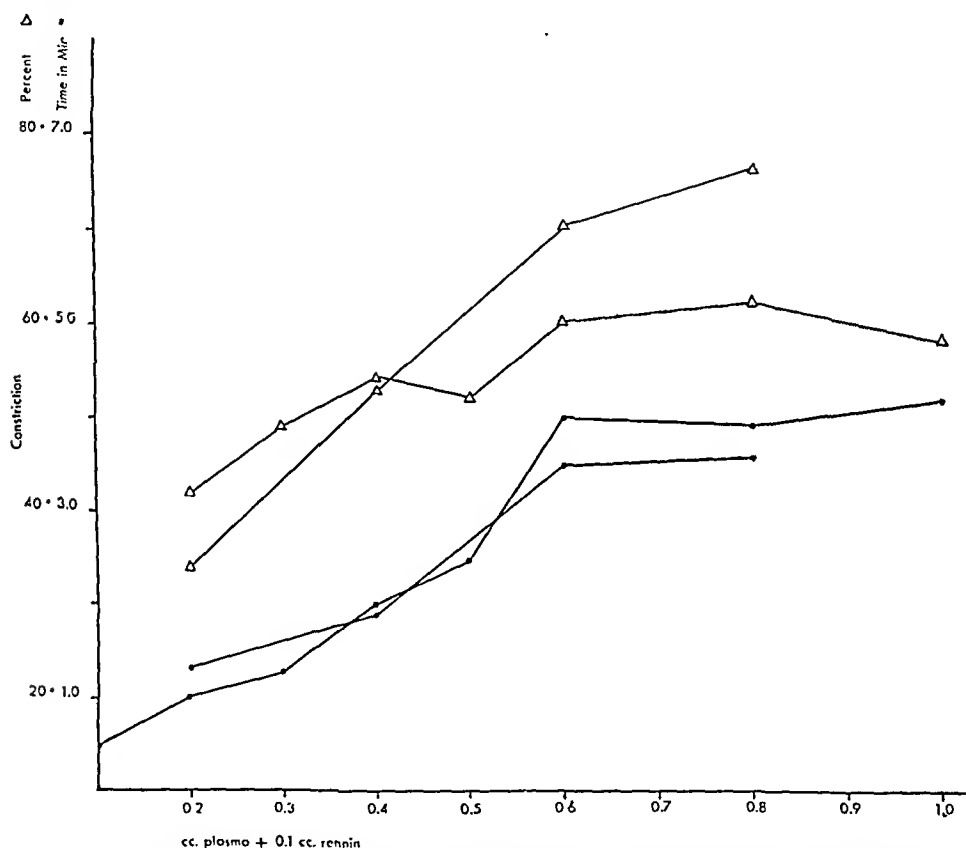


Fig. 7.—Relationship between vasoconstriction (percentage reduction of drop rate and time of reduction) and plasma-renin mixtures in which the renin is constant and the amount of plasma varied. These represent assays performed with the same renin-plasma mixture on the ears of two rabbits.

The first injection of angiotonin caused sharp vasoconstriction, the second, less, and the third, usually none. The addition of a small amount (0.2 c.c.) of plasma to the angiotonin restored the initial vasoconstrictor action.

When it was desired to ascertain the amount of renin- or angiotonin-activator in plasma, a standard amount of renin was mixed with increasing amounts of plasma until a level was reached at which further addition of plasma caused no marked increase in vasoconstriction (Fig. 7).



To compare one plasma with another for a semiquantitative estimation of activator, fixed amounts (0.2 c.c.) of plasma were mixed with excess, fixed amounts of renin; then the mixture was incubated for ten minutes and injected. Since renin was present in excess, if greater amounts of activator were present in one than in the other plasma, greater vasoconstriction resulted from the sample with the greater amount of activator.

TABLE I

THE COMPARATIVE VASOCONSTRICTOR ACTION OF PLASMA AND SERUM FROM A HYPERTENSIVE\* DOG (NO. 9-73), AND THE EFFECT OF HEMOLYSIS

|  | DURATION OF<br>REDUCTION OF<br>FLOW<br>(MIN.) | REDUCTION OF<br>FLOW<br>(%) |
|--|---|-----------------------------|
| <i>Ringer's solution perfused</i>              |   |                             |
| 0.2 c.c. plasma                                | 0   | 0                           |
| 0.2 c.c. serum                                 | 0   | 0                           |
| 0.2 c.c. plasma slightly hemolyzed             | 0.25  | 12                          |
| 0.2 c.c. plasma grossly hemolyzed              | 0.5   | 18                          |
| <i>Arenal blood perfused</i>                   |   |                             |
| 0.2 c.c. plasma                                | 4   | 61                          |
| 0.2 c.c. serum                                 | 4.5   | 64                          |
| 0.2 c.c. plasma slightly hemolyzed             | 5.5   | 75                          |
| 0.2 c.c. plasma grossly hemolyzed              | 7.5   | 79                          |
| 0.2 c.c. plasma                                | 4.25  | 60                          |
| <i>Second rabbit's ear</i>                     |   |                             |
| 0.2 c.c. plasma from a second hypertensive dog | 6.25  | 47                          |
| 0.2 c.c. serum from a second hypertensive dog  | 6   | 50                          |

\*Silk perinephritis method.

The amount of renin in blood may be estimated by the addition of plasma containing activator or concentrated activator prepared from blood, until further addition causes no further increase in vasoconstriction. Hemolyzed erythrocytes appear to contain renin-activator and a vasoconstrictor as well, and for this reason hemolysis must be prevented (Table I).

#### DETERMINATION OF PERIPHERAL VASOCONSTRICTOR SUBSTANCE

It has been shown that plasma from patients with hypertension and from dogs with experimental hypertension causes marked vasoconstriction in the rabbit's ear when the ear is perfused with blood from dogs from which both kidneys have been removed eighteen or more hours before.<sup>10</sup> Blood from such animals we have called "arenal blood" for convenience.

Either plasma or serum may be employed for this assay (Table I). Hemolysis greatly increases their vasoconstrictor action, and hence must be avoided. Plasma which is free of hemolyzed cells and has been kept sterile in the refrigerator does not decrease in potency for at least four days.

The arenal blood used to perfuse the rabbit's ear may be drawn from the dog twelve to eighteen hours after nephrectomy (Table II). The results show that, even after marked retention of urinary excretory products has occurred, the blood is suitable for perfusion.

TABLE II

VASOCONSTRICTOR ACTION OF HYPERTENSIVE PLASMA WHEN INJECTED INTO PLASMA DRAWN AT VARIOUS INTERVALS AFTER NEPHRECTOMY

| TIME AFTER NEPHRECTOMY BLOOD DRAWN FOR PERFUSION (DAYS) | AMOUNT OF PLASMA INJECTED (C.C.) | INITIAL FLOW PER MINUTE (DROPS) | DURATION OF REDUCTION OF FLOW (MIN.) | REDUCTION OF FLOW (%) | TIME AFTER BLOOD DRAWN FROM HYPERTENSIVE DOG* (B.P. = 170) (HOURS) |
|---|----------------------------------|---------------------------------|--------------------------------------|-----------------------|--|
| 1   | 0.2                              | 18                              | 3.25                                 | 60                    | 1  |
| 2   | 0.2                              | 28                              | 3                                    | 47                    | 1  |
| 2   | 0.2                              | 20                              | 2.5                                  | 53                    | 24   |
| 3   | 0.2                              | 26                              | 2.5                                  | 51                    | 1  |
| 3   | 0.2                              | 22                              | 3                                    | 57                    | 24   |
| 3   | 0.2                              | 22                              | 3                                    | 53                    | 48   |
|   |                                  |                                 |                                      |                       | From a normal dog after renin injection                            |
| 1   | 0.2                              | 16                              | 3                                    | 58                    | 1  |
| 2   | 0.2                              | 22                              | 3                                    | 50                    | 24   |
| 3   | 0.2                              | 24                              | 3                                    | 44                    | 48   |
|   |                                  |                                 |                                      |                       | From a hypertensive* dog (B.P. = 190)                              |
| 1   | 0.2                              | 30                              | 4.25                                 | 64                    | 48   |
| 1   | 0.2                              | 28                              | 4.25                                 | 60                    | 24   |
| 1   | 0.2                              | 30                              | 4.25                                 | 64                    | 24   |

\*Silk perinephritis method.

## EVALUATION OF RESULTS

Samples of 0.2 c.c. of plasma, whether from normal or hypertensive patients or animals, when perfused with Ringer's solution, should not cause appreciable constriction, i.e., not greater than 25 per cent for two minutes. Renin alone should cause no constriction, but the mixture with plasma may elicit vasoconstriction of 60 to 80 per cent, lasting from three to six minutes.

When arenal blood is used as the perfusing medium, the injection of plasma from normotensive subjects should cause a maximum of 25 per cent constriction for two minutes. Usually the effect is less marked, i.e., a constriction of 15 per cent, lasting one minute. Plasma from hypertensive subjects causes a constriction of 40 to 70 per cent, lasting three to six minutes (Table III).

Since there is some variation in the results obtained on different ears, it is desirable to repeat the assay on at least two ears, and usually on the same ear twice. When the effects of various procedures are being tried on patients or animals, several determinations on *different ears*

suffice, for ordinarily there is not a great variation when the test is carried out skillfully. It is always desirable to control each series of determinations by the use of plasma from a normotensive subject.

TABLE III

TYPICAL EXAMPLE OF THE REPRODUCIBILITY OF THE VASOCONSTRICTION RESULTING FROM PERFUSION OF PLASMA (0.2 c.c.) OF A HYPERTENSIVE DOG (SILK PERINEPHRITIS) WITH ARENAL BLOOD ON 14 OCCASIONS

| DATE   | AV. MEAN<br>B.P.<br>(MM. HG) | REDUCTION OF FLOW IN |    |                     |    |
|--------|------------------------------|----------------------|----|---------------------|----|
|        |                              | NORMOTENSIVE CONTROL |    | HYPERTENSIVE PLASMA |    |
|        |                              | MIN.                 | %  | MIN.                | %  |
| June 3 | 184                          | 1.75                 | 10 | 4.5                 | 47 |
| 5      | 160                          | 1                    | 8  | 3.75                | 40 |
| 10     | 188                          | 1.5                  | 16 | 3                   | 37 |
| 13     | 180                          | 2                    | 17 | 3.5                 | 50 |
| 15     | 174                          | 1.5                  | 13 | 3                   | 41 |
| 16     | 180                          | 1                    | 16 | 2.5                 | 45 |
| 20     | 180                          | 1                    | 18 | 3.5                 | 41 |
| 23     | 200                          | 1                    | 8  | 3                   | 47 |
| 24     | 188                          | 1.25                 | 20 | 5.5                 | 47 |
| 26     | 186                          | 1                    | 17 | 4                   | 34 |
| 27     | 198                          | 1.75                 | 17 | 3.25                | 47 |
| July 7 | 202                          | 1                    | 19 | 3                   | 45 |
| 8      | 204                          | 1.25                 | 25 | 5                   | 47 |

*Tachyphylaxis After Repeated Perfusion of Angiotonin.*—When Ringer's solution is employed to perfuse an ear, and angiotonin (0.2 c.c.) is injected, vasoconstriction results. The dose which is given directly after the initial drop rate has been resumed usually produces a much smaller constriction, and the third or fourth may elicit none at all. Ears vary considerably in this respect; some require as many as nine or more doses of angiotonin. The injection of a small amount (0.2 c.c.) of plasma, or the filtrate from boiled plasma, either mixed with angiotonin or given just before the angiotonin, restores the vasoactivity of the angiotonin. If, instead of administering plasma, a rest of forty-five minutes is allowed, full activity reappears.

When blood is substituted for the Ringer's solution, tachyphylaxis does not occur nearly so quickly, but does so eventually. A rest period of thirty to forty-five minutes restores reactivity (Table IV), but then tachyphylaxis develops readily when more angiotonin is administered.

It would seem reasonable to conclude from these experiments that the refractory state induced by repeated injections of angiotonin is due to exhaustion of some substance in the walls of the blood vessels, the precursor of which, or the substance itself, is contained in blood plasma. This is the substance we have conceived of as angiotonin-activator. It is our hypothesis that this substance, or its precursor, is in the blood vessel walls, because rest restores vasoconstrictor activity when angiotonin is injected, even though no source is available, i.e., when

Ringer's solution is used as the perfusion medium. That it must be incorporated into the protoplasm of the cells of the vessel walls is suggested by the fact that tachyphylaxis develops when injections of angiotonin are given repeatedly and in quick succession, even though blood—a source of activator—is immediately available.

TABLE IV  
EFFECT OF REST PERIODS ON THE OCCURRENCE OF ANGIOTONIN TACHYPHYLAXIS

| AMOUNT OF ANGIOTONIN<br>(C.C.) | EAR PERFUSED WITH NORMAL DOG'S BLOOD |                                     |                          |
|--------------------------------|--------------------------------------|-------------------------------------|--------------------------|
|                                | DROP RATE                            | LENGTH OF<br>CONSTRICTION<br>(MIN.) | REDUCTION OF<br>FLOW (%) |
| 0.5                            | 29                                   | 5                                   | 69                       |
| 0.5                            | 17                                   | 6                                   | 83                       |
| 0.5                            | 16                                   | 5.5                                 | 58                       |
| 0.5                            | 10                                   | 6                                   | 42                       |
| 0.5                            | 17                                   | 7.25                                | 57                       |
| 0.6                            | 11                                   | 7                                   | 59                       |
| <i>Rest 45 min.</i>            |                                      |                                     |                          |
| 0.5                            | 11                                   | 8                                   | 73                       |
| 0.5                            | 9                                    | 3.75                                | 37                       |
| 0.5                            | 9                                    | 0                                   | 0                        |
| <i>Rest 30 min.</i>            |                                      |                                     |                          |
| 0.5                            | 14                                   | 7.5                                 | 67                       |
| 0.5                            | 10                                   | 0                                   | 0                        |
| <i>Rest 30 min.</i>            |                                      |                                     |                          |
| 0.5                            | 13                                   | 6.5                                 | 50                       |
| 0.5                            | 13                                   | 1.5                                 | 27                       |
| 0.5                            | 9                                    | 0                                   | 0                        |
| <i>Rest 30 min.</i>            |                                      |                                     |                          |
| 3.0                            | 13                                   | 5.5                                 | 47                       |

Since refractoriness develops from repeated injections of angiotonin, it is important to avoid repeating them too frequently if reproducible results are to be expected. A rest period of ten to fifteen minutes usually suffices after the drop rate has returned to its initial value following vasoconstriction.

#### SUMMARY

A method for perfusing isolated organs, especially rabbits' ears, with blood or Ringer-Locke's solution, under pulsatile pressure, has been described. Its applications to the assay of blood samples containing renin, renin- and angiotonin-activator, and the angiotonin-like vasoconstrictor action of peripheral blood are recorded.

Tachyphylaxis to angiotonin in the rabbit's ear may be established by repeated, frequent injections, and the tachyphylaxis may be overcome by additions of either plasma or boiled plasma filtrate to the injected angiotonin, or by a rest period. It is suggested that angiotonin tachyphylaxis is in part due to exhaustion of a heat-stable substance, or its precursor, which is contained in plasma and is necessary for vasoconstriction. The cells in the wall of the blood vessel can either syn-

thesize this substance, or absorb the necessary constituents from Ringer's solution, for rest, while the ear is being perfused with Ringer's solution, abolishes tachyphylaxis.

I wish to express my sincere appreciation to Mrs. Marian Norman, John Tilden, and Mr. Clifford Wilson for their aid in this investigation.

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# THE VALUE OF CARBON DIOXIDE BATHS IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE AND ALLIED CONDITIONS

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## INTRODUCTION

FOR over half a century, carbon dioxide baths have been employed in the management of vascular disease. The dissolved gas, because of its solubility in both the watery and fatty constituents of the skin,<sup>1-3</sup> diffuses through the dermal layers, thus coming into intimate contact with the network of small blood vessels and causing them to dilate. The rationale for the use of carbon dioxide in cardiac and peripheral vascular diseases depends upon this specific vasodilating effect.<sup>4, 5</sup>

In order to convince ourselves of the claims which have been made in its behalf, investigations along related clinical and experimental lines were undertaken.

## TECHNIQUE OF ADMINISTRATION

A concentration of 1 to 4 Gm. of carbon dioxide per liter of solution is essential for the production of the maximum therapeutic effect.<sup>6</sup> Natural springs, like those at Nauheim and St. Moritz, contain this optimum concentration, but in hospitals it is necessary to employ artificial methods involving either the introduction of already prepared gas into solution, or the introduction of chemical substances to form the gas in the bath. In the first instance, the gas is led from the tank to the bottom of the bath, where it is dispersed through the water from a wide-surfaced nozzle with multiple, fine apertures; in the latter method, which is the technique employed at Montefiore Hospital, measured amounts of acid and alkali are brought together, liberating carbon dioxide gas. The necessary quantities are readily calculated from the molecular weights. In practice, about 0.5 pound of ordinary commercial sodium bicarbonate and 200 c.c. of commercial hydrochloric acid in a total volume of 40 liters of water are used. There need be no fear of the presence of unneutralized acid with these proportions; as a matter of fact, there should still be a slight excess of alkali in the bath at the end of treatment.

Our experience has shown that the most suitable and inexpensive containers for the bath are water-tight wooden barrels\* of 40-liter capacity. The barrel is filled with tap water at a temperature varying between 32° and 36° C., which is just comfortable for the extremities. Higher temperatures are not employed because they would exert a direct thermal effect on the limb and also retard the passage of the gas from the solution.

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\*A pickle barrel, thoroughly cleaned, is admirably suited for this purpose.

The bicarbonate is thrown in and dissolved with a few swirls of the hand; the patient sits comfortably on a high stool or wheel chair and places his legs in the bath, immersing them to the knees. Ulcerations may be covered with a thin layer of vaseline in order to prevent direct contact with the solution, which sometimes causes pain. The acid is then siphoned\* into the bath well below the surface of the water, so that the chemical reaction takes place near the bottom of the barrel. By introducing the acid slowly in this way, the evolution of gas is also slow, and the extremities are exposed in their entirety to fine bubbles of carbon dioxide gas. A turbulent reaction which comes to an end soon after mixing is not desirable.

At the end of one-half hour, the extremities are carefully dried and oiled, and then gentle massage may be instituted. As the legs emerge from the bath, the skin is reddened; the color varies from a pale rose to a bright pink. The skin is slightly warm, although the bath itself is of an indifferent temperature. There is a sharp line of demarcation corresponding to the level to which the limbs are immersed. Other effects often noted are disappearance of the shiny glaze of atrophic skin, as well as an increase in softness and elasticity of the skin itself, and an increase in the firmness of the subcutaneous tissue. These changes are most marked after several weeks of treatment and are due, in part, to the better nourishment of the skin and, in part, to massage or other concomitantly used physical measures. The hyperemia usually disappears shortly after removal from the bath but may persist for one-half hour or longer. The immediate subjective results from one bath are not very striking, but, after a course of daily treatment lasting from one to two weeks, the pain of ischemia, whether at rest or on motion, is often diminished or has disappeared. The treatments may be repeated several times each day. In fact, the patient may be taught to administer the baths himself at home, after the danger of using acid solutions has been explained. No expensive or complicated and cumbersome machines are required for its administration, and many individual treatments can be given in a busy department with a minimum of effort.†

#### CLINICAL INVESTIGATIONS

The following procedures were carried out on representative groups of patients, some with normal peripheral vessels and others with varying degrees of peripheral vascular disease.

*Capillary Microscopy.*—The skin of treated regions in the extremities of thirty patients was examined directly with the aid of the capillary microscope. The most striking change was the extraordinarily large number of capillary tufts and loops which had become visible; there were many more than had been seen in the same area before exposure to carbon dioxide. In addition, the lumina of both the arterial and venous limbs of the capillaries were larger and contained blood which was brighter in color (presumably better oxygenated) than prior to treatment (Fig. 1). The blood flow in many of the capillaries was distinctly accelerated, so that the granular appearance of slowly cir-

\*Commercial hydrochloric acid is diluted three times with tap water and stored in the large, brown gallon bottle in which this acid originally comes. A simple siphon arrangement of glass and rubber tubing facilitates handling. Since about 600 c.c. of the diluted acid are used per treatment, the storage bottle may be marked off appropriately to give enough acid for six or seven treatments.

†An indication of the popularity of this mode of treating vascular disease of the extremities at the Montefiore Hospital is readily seen from the statistics. In 1940, approximately 4,000 hydrotherapeutic treatments were given in the physical therapy department. Of these, almost 1,500 were carbon dioxide baths.

culating blood, when individual corpuseular elements can be discerned, was lost. The flow in the larger tributaries, the so-called "venous sinuses" which are situated more deeply in the skin, was also speeded up. The treatment hastens the emptying of their slow-moving cyanotic blood and contributes to the more efficient delivery of arterial blood to the tissues. The changes just described are characteristic of active hyperemia.

Although with this method of clinical observation only superficial vessels are clearly visualized, the increased redness of the background indicates that deeper vessels in the subpapillary plexuses and in the subcutaneous tissues are probably also involved in the reaction. This corroborates the observations of Hirsch<sup>7</sup> and Benatt and Honighaus.<sup>8</sup> Most investigators feel that the vasodilatation is due to a direct chemical influence upon the muscle elements of the vessel walls; however, the possibility that it may be the result, in whole or in part, of a vascular axon reflex must also be borne in mind.

*Skin Temperature.*—In general, it may be said that with active hyperemia and an increase in blood flow a rise of local temperature occurs. For this reason, the skin temperature of treated extremities was observed and charted by means of a thermocouple and galvanometer. Eleven patients form the basis of these observations; nine had peripheral vascular disease of the arteriosclerotic type, and two served as normal controls. Inasmuch as the results were approximately the same in all cases, only one will be presented in detail (Fig. 2). In each instance, control readings were taken at the same area under the basal experimental conditions, i.e., room temperature, time of day, period of rest, etc., but with tap water instead of the carbon dioxide bath.

Regardless of the nature of the bath, whether tap water or carbon dioxide, there is a sharp rise in the skin temperature of the toe shortly after immersion; this rise approximates closely the temperature of the bath. As soon as the limbs are withdrawn there is a sharp fall in skin temperature; this is most marked during the first five minutes. After the initial drop, the fall is more gradual, and, in the case of the carbon dioxide treated extremity, it is usually from one-half to one and one-half hours before the skin temperature of the toe returns to its basic resting level. When tap water is used under similar conditions, this resting level is reached in a much shorter time, usually from five to twenty minutes after removal from the bath.

The maintenance of a few degrees ( $1^{\circ}$  to  $3^{\circ}$ ) of temperature elevation for one-half to one and one-half hours does not appear to be startling evidence of the effectiveness of carbon dioxide. It must be remembered, however, that under normal conditions the exchange of heat between the skin and surrounding air is quite rapid, and is a manifestation of the temperature-regulating function of that organ. This is especially



true of the distal areas, such as the finger tip or the base of the toes, where there are unusually large numbers of arteriovenous anastomoses. Even when extremities are exposed to prolonged heating, the surface temperature falls rapidly once the source of the heat is removed. The persistence of a mild temperature rise for a variable period after exposure to carbon dioxide assumes a greater significance in the light of these facts. In all probability it means that the vasodilating factor remains present and active in the tissues for an appreciable length of time.

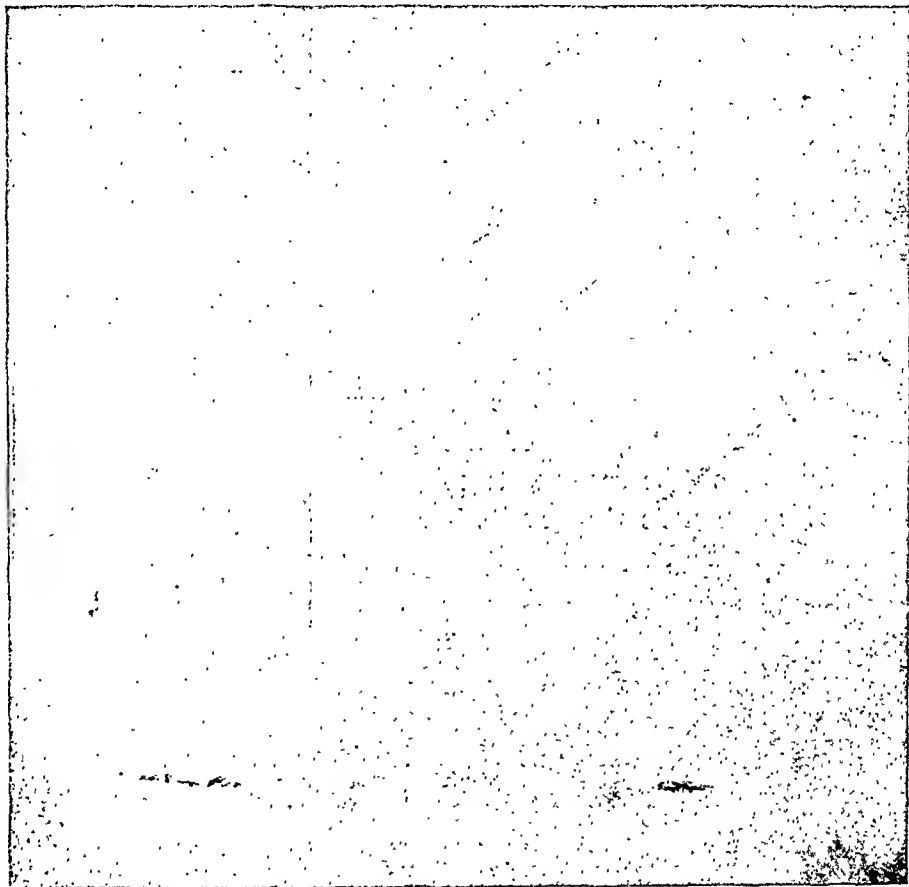


Fig. 14.—Capillaries of the nail fold before treatment with carbon dioxide. Photomicrograph from the finger of Mrs. F. N., aged 43 years, who had mild vascular disease of the lower extremities, but whose upper extremities were clinically normal.

*Plethysmography.*—As a result of vasodilatation, there is an increase in limb volume. The increase represents the additional amount of circulating blood present in the vascular channels, and an additional store of nutritive substance for tissue use. Although such studies have been employed in the past,<sup>9</sup> they were undertaken again with the hope that they might furnish a quantitative measure of the effectiveness of carbon dioxide.

Portions of the lower extremity approximately 10 inches in length, including the bulk of the calf muscles, were enclosed in a water-tight

plethysmograph of the type used by Lewis and Grant<sup>10</sup> and adapted for use on the leg. Each limb segment was kept in contact for one-half hour with a carbon dioxide bath generated in the plethysmograph. At the end of this period, the bath was rapidly siphoned off and replaced immediately by tap water of the same temperature. Blood inflow curves were taken before and after the development of the skin hyperemia, using the well-known method of Hewlett and Van Zwaluwenberg.<sup>11</sup>

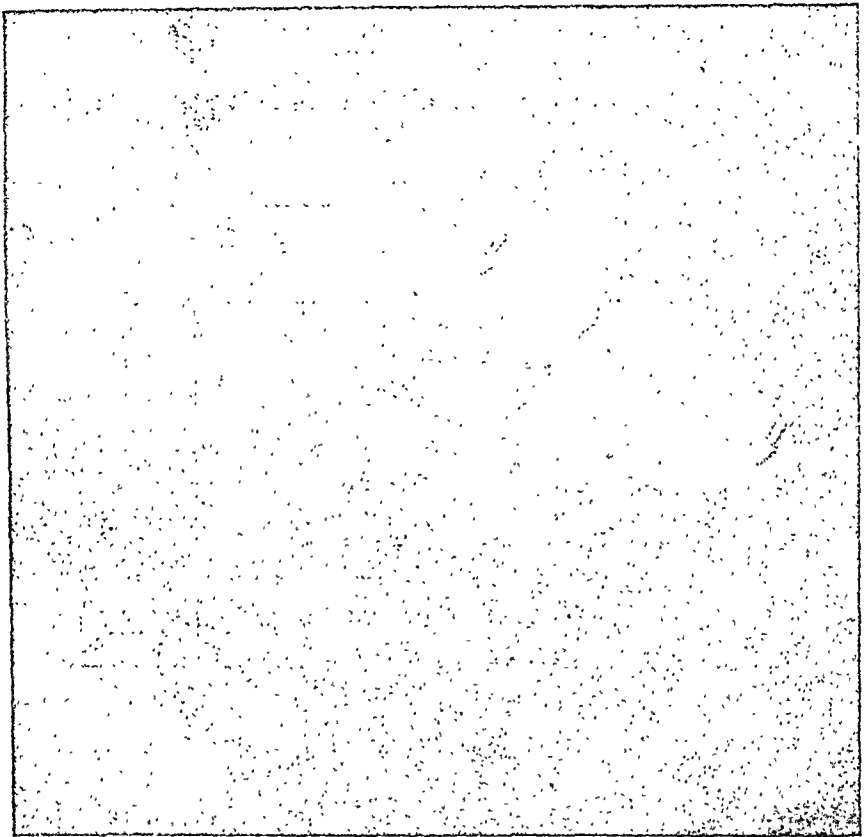


Fig. 1B.—Capillaries of the nail fold after exposure to a carbon dioxide bath for one-half hour. Notice the increase in the number of capillaries as well as the dilatation of these vessels (arrows). Photomicrograph from the finger of Mrs. F. N.

A collecting pressure of 40 to 70 mm. Hg\* was thrown into the cuff proximal to the plethysmograph. As early investigators<sup>11</sup> have shown, when the venous circulation is suddenly occluded by a pressure of this magnitude, which, of course, does not impede arterial flow, the increase in limb volume can be considered as the arterial inflow. Certain technical precautions<sup>10</sup> must be heeded, however, if reliance is to be placed on the results. The inflow can be registered graphically, and, since the area of the limb segment enclosed is readily ascertained, the amount of blood flow per unit of time per 100 c.c. of tissue is therefore known.

\*The pressure used was the one which gave the optimal blood inflow in the control curve.

TABLE I

| CASE | NAME  | AGE<br>(YR.) | SEX | DIAGNOSIS           | CLINICAL FEATURES   | BLOOD INFLOW<br>(C.C./100 C.C.<br>TISSUE<br>PER MIN.) |                 | COMMENT   |
|------|-------|--------------|-----|---------------------|---|---|-----------------|---|
|      |       |              |     |                     |   | CON-<br>TROL  | CO <sub>2</sub> |   |
| 1    | H. K. | 30           | F   | Ulcerative colitis  | Extremities normal  | 2.3   | 5.7             | About 150% increase in blood flow maintained for 30 min. after CO <sub>2</sub> bath   |
| 2    | D. T. | 22           | M   | Multiple sclerosis  | Extremities normal  | 2.0   | 3.2             | Approximately 60% increase in blood flow  |
| 3    | G. W. | 23           | M   | Multiple sclerosis  | Extremities normal  | 4.6   | 5.3             | Approximately 15% increase in blood flow  |
| 4    | H. J. | 42           | M   | Parathyroid disease | Extremities normal  | 2.6<br>2.2  | 3.9<br>3.7      | Approximately 55% to 70% increase in blood flow   |
| 5    | S. M. | 47           | M   | Portal cirrhosis    | Extremities normal  | 2.0   | 2.0             | No change in blood inflow after treatment. Although the patient's peripheral circulation appeared grossly normal, it may be that his lack of response was due to the inhibiting effect of hepatic toxins on his smaller blood vessels |
| 6    | S. R. | 46           | M   | Raynaud's syndrome  | Spontaneous amputation of several fingers and toes in the past; pale and cold hands and feet which become a slate-blue during cold weather; all peripheral arteries patent; good collateral circulation | 1.8   | 3.1             | Approximately 70% increase in blood flow  |

| 7  | L. A.  | 60 | M | Scleroderma  | Typical leathery appearance of skin, associated with tightness which was most marked over joints | 0.42 | 0.91 | Good response to CO <sub>2</sub> , with approximately 100% increase in blood flow. The low absolute values were probably due to inability to increase limb volume because of tightness and inelasticity of skin |
|----|--------|----|---|--|--|------|------|---|
| 8  | M. Ku. | 55 | M | Arteriosclerotic peripheral vascular disease; pulmonary tuberculosis         | Only femoral and popliteal vessels patent; good collateral circulation                           | 2.8  | 5.5  | Approximately 100% increase in blood flow   |
| 9  | E. H.  | 66 | F | Peripheral vascular disease; arteriosclerosis; diabetes; peripheral neuritis | Only right femoral artery patent; good collateral circulation                                    | 2.2  | 4.3  | Approximately 100% increase in blood flow   |
| 10 | J. Y.  | 68 | M | Peripheral vascular disease; arteriosclerosis; diabetes                      | Femoral artery patent; fair collateral circulation   | 3.2  | 5.4  | Approximately 70% increase in blood flow  |
| 11 | J. S.  | 68 | M | Peripheral vascular disease; arteriosclerosis                                | Left femoral artery patent; cold skin and livid cyanosis of feet                                 | 1.1  | 2.0  | Approximately 100% increase in blood flow   |
| 12 | D. B.  | 70 | F | Peripheral vascular disease; arteriosclerosis; diabetes                      | Femoral and popliteal vessels patent   | 2.9  | 3.7  | Approximately 25% increase in blood flow  |
| 13 | B. F.  | 54 | F | Peripheral vascular disease; arteriosclerosis; diabetes                      | Femorals and right popliteal vessels patent  | 0.99 | 1.4  | Approximately 40% increase in blood flow  |
| 14 | J. W.  | 50 | F | Peripheral vascular disease; arteriosclerosis; diabetes                      | Only femoral and popliteal vessels patent  | 4.9  | 5.5  | Approximately 15% increase in blood flow  |
| 15 | M. Kc. | 63 | M | Peripheral vascular disease; arteriosclerosis                                | Only femoral and popliteal vessels patent  | 2.9  | 6.3  | Approximately 125% increase in blood flow   |

Such procedures were carried out on extremities which were the seat of peripheral vascular disease, as well as on normal controls (Table I). In general, it may be said that, if a limb becomes hyperemic when exposed to carbon dioxide, there will be, at the same time, an increase in blood flow. This is best seen in the graphic representations (Fig. 3A and B).

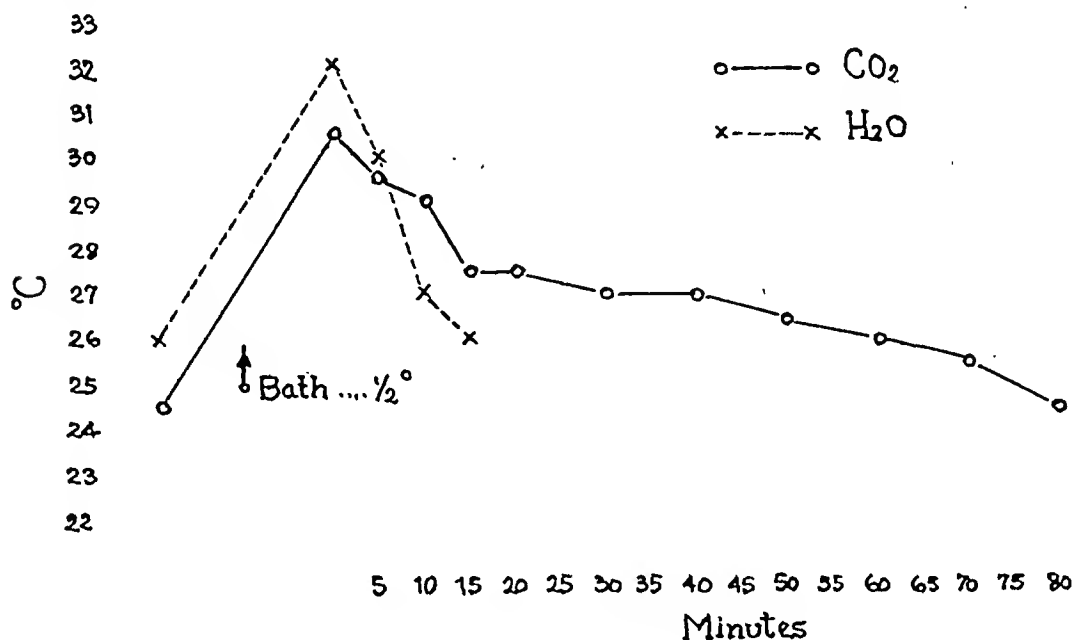


Fig. 2.—Skin temperature of the left great toe. The patient was the same woman whose capillaries are pictured in Fig. 1. The rapid return of the skin temperature to normal shortly after removal from the control bath of tap water and the maintenance of the temperature rise following the carbon dioxide bath are well illustrated. Slight differences in the initial temperature levels of the great toe are physiologic and are to be expected, inasmuch as the test baths were carried out on consecutive days.

Values of 2 to 4 c.c. of blood flow per 100 c.c. of tissue substance per minute are normal for the extremities when flow is estimated by the plethysmographic method.<sup>11</sup> It would seem that these values should be much lower when varying degrees of obliteration of the vascular bed have taken place. That this was not so in most of the peripheral vascular disease cases which we studied is evident from Table I; the inflow figures are well within the normal range. To anyone who can picture the rich collateral circulation which develops in response to the stimulus of tissue anoxemia, this need not come as a surprise. In a previous paper<sup>12</sup> we have shown that simple ligation of the main vessels of the rabbit's ear results in the development and widespread ramification of the smaller caliber vessels in that ear in a relatively short time. Allen and Camp<sup>13</sup> have shown by means of arteriographic studies that the same process occurs in the human being. Indeed, in an occasional case, the channels may be so well developed that the rate of blood flow to the tissues may be well above normal (Table I, Case 14).

In the few instances in which the inflow rates were low (Table I, Cases 11 and 13), the degree of vascular change, when measured by the usual clinical methods, was so extensive as to indicate very little

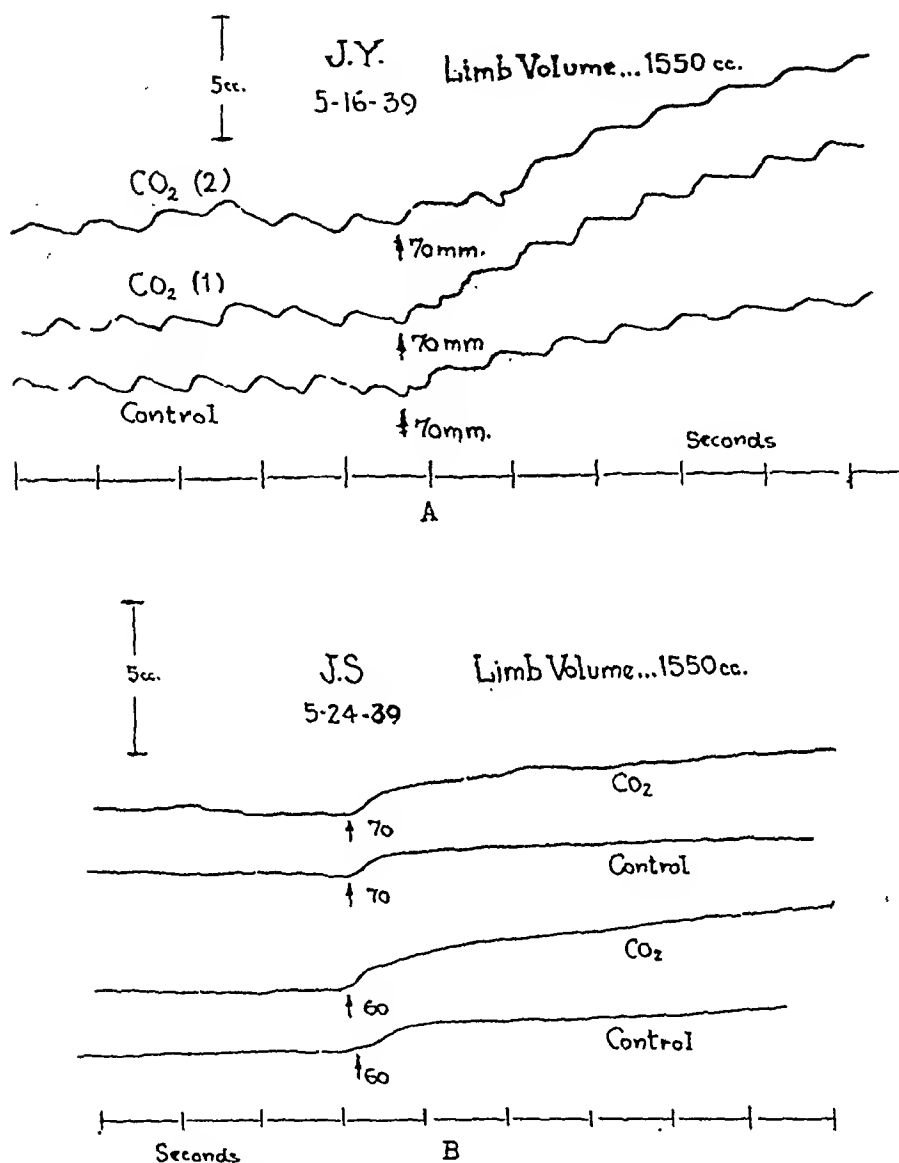


Fig. 3.—Inflow curves (plethysmograms) from the leg. A, Case 10 (Table I). A comparison of the lowest or control curve (water bath) with the two upper curves (after exposure to carbon dioxide in the plethysmograph for one-half hour) shows an increase in blood inflow of 70 per cent, a rise of from 3.2 c.c. blood per 100 c.c. tissue volume per minute to 5.4 c.c. per 100 c.c. per minute. The arrow and the number adjacent indicate the point at which 70 mm. Hg pressure was placed on the extremity. Note that individual pulse waves are present in this graph. B, Case 11 (Table I). In this patient the disease process was so advanced that there was only a "nonpulsating" circulation in the legs. This is confirmed by the absence of pulse waves in the graph. Despite this, a comparison of the inflow curves shows an increase of blood flow after the carbon dioxide bath. This approximates 100 per cent (1.1 c.c. blood inflow to 2.0 c.c.).

reserve. No pulse wave was visible in the plethysmographic curve obtained from such patients. In their extremities, the metabolic demands must be supplied by "nonpulsating circulation" of small, fine caliber

vessels, and by pathologically patent arteriovenous anastomoses. Neither group of vessels is capable of supplying large amounts of blood directly to the tissues under times of stress.<sup>14</sup> The peripheral circulation under such conditions cannot be described in terms of blood flow, but more properly as a sort of "seepage."

In any event, regardless of the absolute values for blood flow, or the nature and extent of the underlying pathologic process, there was an increase in blood flow of 15 per cent to 150 per cent in the extremity treated with carbon dioxide. This increase must obviously be a beneficial influence; it means better tissue nourishment, as well as more adequate removal of tissue metabolites.

Although the blood flow is moderately increased in most cases, in all probability the increase is due to an effect primarily on the skin and other superficial vessels. This is in sharp contrast to the work of earlier investigators,<sup>4, 16</sup> who maintained that there was a profound effect on the deeper and larger caliber vessels. There can be little question that, if such were the case, the increase in blood flow would of necessity be of far greater magnitude.

#### DISCUSSION

The increasing interest in chronic disease has driven home one salient point—the danger of so-called "vigorous treatment." It is a matter of common knowledge that an organ which is no longer young and elastic cannot accommodate itself readily to extreme changes as well as a perfectly functioning unit. Thus, intensive antisiphilitic therapy may cause irreparable damage in an otherwise symptomless case of tertiary syphilis; or repeated and profound diuresis may cause an ailing heart and overworked kidneys to go further into failure.

In organic peripheral vascular disease, which is the chronic disease par excellence, this is doubly true. Measures designed to produce vasodilatation or to stimulate the formation of collateral channels may defeat their very purpose by increasing the metabolism of the tissues to such an extent that it is impossible to satisfy their needs, even if all of the vessels available were in use. An increase in pain may ensue, and the possibility of tissue death and necrosis is enhanced. It is for this reason that such measures as local heating, shock therapy, and hyperpyrexia, although still widely used, have fallen into disrepute in the treatment of the elderly patient or of patients with extensive vascular disease. These modalities are not for everyday use; they belong in the realm of him who is trained in the treatment of peripheral vascular disease.

In carbon dioxide we have a therapeutic agent which produces vasodilatation and increased blood flow without increasing tissue metabolism

or the work of the heart and other vital organs.\* The usual ambulatory patient, perhaps a man 50 to 60 years old, who has mild diabetes and a history of cramps in the calves of both legs, with consequent disability, who shows feeble or absent pulsations and oseillometric readings, and has a fairly good compensatory circulation, as revealed by clinical tests, may derive much benefit from treatment with carbon dioxide baths. Such treatment does not cure the underlying disease, of course, but it frequently relieves the signs of circulatory insufficiency, i.e., pain, rubor, cyanosis, and atrophy of the skin.

It is not a cure-all for vascular disease of the extremities. Other forms of therapy may prove more efficient in a given case, and patients may fail to respond favorably to carbon dioxide in spite of a bright red hyperemia of the skin. If carbon dioxide is used primarily with the intention of developing and maintaining collateral circulation, it is a welcome addition to our armamentarium. There are also contraindications to its use, of course. Deep, open wounds, purulent infections, and dry gangrenous processes are chief among these.

Clinical studies indicate that carbon dioxide has a definite surface effect, and, in all probability, some action on deeper structures, also. A priori, it would appear that its use would be of value in several conditions which are commonly included in the realm of peripheral vascular disease.

First and foremost are the superficial ulcerations and necroses which are so frequently caused by local arteriolar closure (arterioles and small arterial branches) or varicose veins. These lesions vary in extent but commonly involve only several layers of the skin, possibly with the superficial portion of subcutaneous tissue. We have been agreeably surprised in many cases, in some of which the lesions were refractory to the more generally used methods of treatment, by the prompt healing which took place.

It has also been used in vasospastic conditions, such as the group of disorders comprising the so-called Raynaud's syndrome, as well as in generalized arterial disease of undetermined etiology and thromboangiitis obliterans. With the removal or counterbalancing of the spasm, subjective and objective improvement has followed. In these conditions, as well as in others, carbon dioxide is only an alternative type of treatment; there are other methods which may be more effective.

In vasoparetic disorders, such as acrocyanosis and erythromelalgia, its use may also produce surprisingly good results.

Finally, it has been employed in several cases of scleroderma. Inasmuch as the diseases seen in a hospital for chronic disease are, without

\*These remarks concern the action of carbon dioxide upon the extremities. When the entire body is immersed in a carbon dioxide bath, various mechanical, thermal, and reflex factors must be considered. For the sake of brevity they have not been included in this paper, but they are described in detail in an article by Harpuder<sup>2</sup> on experimental balneotherapy.



exception, of extremely long standing, little more than subjective relief could be expected. All of these patients had the typical mummification of the skin, as well as sclerodactylia. It is our belief that, early in the disease, there might be a synergistic action between a method of general treatment, such as the carbon dioxide body bath, and the local application of histamine or mecholyl iontophoresis,<sup>15</sup> which would heighten the benefits to be obtained.

#### SUMMARY AND CONCLUSION

Carbon dioxide, by virtue of its chemical properties, is capable of producing active hyperemia when in intimate contact with the body surface. This hyperemia is localized to the area treated and is unaccompanied by an appreciable rise in tissue or general metabolism. The carbon dioxide bath does cause an increase of blood flow, which, we assume, is chiefly in the superficial layers of the subcutaneous tissue and the skin. No proof can be given at this time of deeper penetration or action. As a result of this increase in blood flow, the bath is a gentle and effective method of treating a selected group of patients who, in general, are elderly persons with diffuse, far-advanced disease, but have a fairly good collateral circulation in spite of pain, skin and color changes, and occasional superficial necroses. The carbon dioxide bath is a palliative method of treatment which aids in preserving the peripheral circulation by releasing spasm and aiding in the production of compensatory circulation, and by not increasing tissue metabolism.

The use of the carbon dioxide bath is also suggested in refractory cases of superficial necrosis, vasospastic disease, and scleroderma.

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## CENTRAL NERVOUS SYSTEM MANIFESTATIONS IN ACUTE MYOCARDIAL INFARCTION

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RECOGNITION of the clinical characteristics of acute coronary artery thrombosis, with cardiac infarction, has become commonplace since the pioneer work of Herrick.<sup>1</sup> Pain, the most alarming aspect of such seizures, has been emphasized in dramatic language.<sup>1-4</sup> In spite of recent emphasis on the fact that the attacks may be painless, an important reason for overlooking an acute attack is the absence of pain as a major symptom.<sup>5-7</sup> On the other hand, pain in the chest is likely to lead to a diagnosis of cardiac infarction without critical exclusion of other possible causes.<sup>5, 6</sup> Because of the many obstacles in the way of correct interpretation of atypical cases of infarction of the heart we have undertaken a retrospective study of autopsy material. This paper presents a group of cases in which the symptoms indicated acute cerebral disease, but autopsy revealed a recent myocardial infarct and no *acute* cerebral vascular lesion.

### MATERIAL AND METHODS

We have examined the autopsy protocols of all cases of myocardial infarction found in the department of pathology of the University of Cincinnati Medical School for the twenty years ending with 1940 (Table I). The records include material from the pediatric service, and from the Chronic Disease Hospital since 1930. These are the routine autopsy records, compiled by the senior and junior pathologists under the direction of Dr. Richard S. Austin. The criteria for the diagnosis were the same as those used by one of us in a previous study.<sup>7</sup> Doubtful cases were discarded.

In seven\* of the eight cases an acute vascular lesion in the brain was diagnosed because of the neurological symptoms. In only two was an infarct of the heart suspected. In order to establish criteria to exclude the possibility of acute cerebral vascular lesions, it would be desirable to have injection or meticulous dissection of the entire arterial tree of the brain, and multiple sections of certain areas. Such desiderata were not possible in these cases. Since the clinical diagnosis pointed to an acute cerebral vascular lesion, the pathologist was on the lookout for embolus, thrombus, or hemorrhage. It seems improbable that any extensive lesion was missed. Our cases satisfy these criteria: (1) The presenting symptoms were interpreted as arising from an acute cerebral vascular lesion or intracranial disturbance. (2) Arteriosclerosis of the cerebral arteries was advanced (except in Case 4). (3) No hemorrhage, embolus, or thrombus was found in the brain. (4) An infarct of the heart was found. The age of the infarct made it probable that it occurred at the time of the cerebral symptoms.

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\*The eighth case was that of an epileptic.

In the entire series we found eight other cases of recent cardiac infarction, with similar symptoms and clinical diagnosis. They were discarded because the brain had not been examined. In seven instances, unrecognized cardiac infarction occurred in patients with long-standing hemiplegia. In nine, hemiplegia followed cardiac infarction, but in only three was it reasonably certain that a mural thrombus had contributed an embolus. In four additional cases of cerebral and coronary thrombosis it could not be ascertained which came first, or whether they were related.

TABLE I  
INCIDENCE OF MYOCARDIAL INFARCTION

| YEAR | TOTAL AUTOPSIES | MYOCARDIAL INFARCTS | PERCENTAGE |
|------|-----------------|---------------------|------------|
| 1921 | 261             | 0                   | 0.0        |
| 1922 | 249             | 3                   | 1.2        |
| 1923 | 300             | 2                   | 0.7        |
| 1924 | 281             | 2                   | 0.7        |
| 1925 | 306             | 3                   | 1.0        |
| 1926 | 422             | 3                   | 0.7        |
| 1927 | 483             | 13                  | 2.7        |
| 1928 | 553             | 16                  | 2.9        |
| 1929 | 664             | 13                  | 2.0        |
| 1930 | 652             | 21                  | 3.2        |
| 1931 | 601             | 23                  | 3.8        |
| 1932 | 754             | 32                  | 4.2        |
| 1933 | 778             | 43                  | 5.5        |
| 1934 | 887             | 40                  | 4.5        |
| 1935 | 762             | 29                  | 3.8        |
| 1936 | 981             | 65                  | 6.6        |
| 1937 | 1003            | 61                  | 6.1        |
| 1938 | 818             | 44                  | 5.4        |
| 1939 | 715             | 53                  | 7.4        |
| 1940 | 724             | 46                  | 6.4        |
|      | 12,194          | 512*                | 4.2        |

\*White males, 305; colored males, 84; white females, 83; colored females, 40.

Several cases in which there were similar neurological signs and symptoms were found in other forms of heart disease. Most of these were in association with advanced coronary and cerebral arteriosclerosis, and usually with hypertension. In one instance, diffuse interstitial myocarditis (Feidler's) was found. It was suspected, but could not be proved, that these attacks were associated with a sudden fall in blood pressure.

#### REVIEW OF THE LITERATURE

If we omit Hammar's interesting case of coronary embolism with extreme bradycardia and syncope,<sup>8</sup> Huber<sup>9</sup> was the first to stress cerebral manifestations in coronary thrombosis. This made no impression upon the minds of clinicians at that time because it was believed universally that such an event as coronary obstruction was necessarily fatal. Errors of omission in the diagnosis of cardiac infarction have become possible only since the widespread dissemination of knowledge of the usual symptoms of an acute attack. Although in his first paper Herriek<sup>1</sup> remarked that "the mind is nearly always clear," he mentioned cases in which there were mental apathy and marked general weakness.

Similar cases have been observed frequently.<sup>2, 3</sup> White<sup>4</sup> mentioned weakness in older people, and "mental disturbances, faintness, dizziness and even syncope with coma and convulsions. . . . Prolonged coma lasting for hours or even days, especially in aged persons, may rarely follow the temporary or prolonged drop in blood pressure that sometimes accompanies acute coronary thrombosis."

The nature of focal cerebral vascular lesions which follow acute infarction of the heart is not simple, as is often assumed. Hemiplegia after such an attack may arise in at least three ways. The mechanism usually invoked is embolism from a dislodged mural thrombus. Master, Daek, and Jaffe<sup>10</sup> have shown that this is particularly serious in the younger patients. In a series of 300 autopsy cases, one of us<sup>11</sup> found that, of fifteen adequately studied cases in which hemiplegia followed an acute myocardial infarct, only six were embolic in nature. Nine resulted from a local vascular fault; seven of these patients had thrombi, and two had hemorrhages. It is probable that low arterial blood pressure and reduced cerebral blood flow favored thrombus formation. Why hemorrhages should have occurred is obscure.

The time of occurrence of hemiplegia after infarction of the heart is of some help in differentiating thrombosis from embolism. Changes in circulatory dynamics appear soon after damage to the heart. If hemiplegia appears early, it is likely to have been caused by a thrombus or, if transient, by a reduction in effective cerebral circulation. Embolism from dislodged mural clots rarely occurs until after the first week.<sup>11</sup> Dozzi<sup>12</sup> has studied cerebral vascular sequels of coronary thrombosis. Twelve of his forty-one patients had hemiplegia, either thrombotic or embolic, which so masked the picture that the heart lesion was not appreciated. In the other cases the diagnosis was made ante mortem. He did not report the time relationships of the two lesions.

In their comprehensive monograph on carotid sinus syncope, Ferris, Capps, and Weiss<sup>13</sup> clarified at least three possible mechanisms—pulse slowing, fall in arterial tension, and a direct cerebral reflex. Mechanisms similar to the second or third of these might also explain cerebral disturbances after cardiac infarction, with or without a sensitive carotid sinus. If the circulation in the brain is considerably reduced, the resulting symptoms may so distort the clinical picture that the heart is completely overshadowed by focal or general central nervous system manifestations.

In this connection it is well to recall that there is evidence of cerebral disturbances in association with well-recognized abnormalities of cardiac function. The cerebral complications of bradycardia with the Adams-Stokes syndrome are well known.<sup>14</sup> Cerebral symptoms as a result of attacks of tachycardia were recorded as early as 1889 by Bouvert, according to Esmein and Donzelot.<sup>15</sup> In their paper on the syncopeal

form of paroxysmal tachycardia, they reported cases in which a variety of cerebral symptoms were repeated regularly with each attack. They did not observe hemiplegia.

Blackford and Willius<sup>16</sup> described two cases of auricular flutter in which collapse occurred after a period of rapid ventricular activity. Barnes<sup>17</sup> made a special study of the cerebral manifestations of paroxysmal tachycardia. In fifteen of 104 cases there were severe symptoms, such as vertigo, blurred vision, and dizziness. In prolonged attacks these were very severe, and syncope, epileptiform seizures, blindness, and convulsions occurred. The symptoms were particularly severe in patients with cerebral arteriosclerosis.

Another group with central nervous system symptoms caused by cardiac dysfunction was reported by Dumas.<sup>18</sup> He observed a number of hypertensive patients who developed transitory hemiplegia during attacks of left ventricular failure and pulmonary edema. This occurred only when the arterial blood pressure fell during the attack. If the pressure returned to normal, the symptoms disappeared. In those who died, the most striking abnormalities were pulmonary edema and cerebral arteriosclerosis without thrombosis. The hemiplegia was explained as the result of ischemia which made itself felt particularly in areas whose blood supply was already impaired by arterial lesions.

A group with similar symptoms was reported by Fleming and Naffziger.<sup>19</sup> Their patients developed temporary hemiplegia after sudden decreases in arterial blood pressure or a sudden change in position. When they were given adrenalin or other stimulants, the hemiplegia disappeared *pari passu* with the restoration of arterial tension. All of these patients had sclerosis of the cerebral arteries. It was concluded that any precipitous fall in arterial blood pressure, such as that associated with myocardial weakness, surgical shock, or dilatation of the splanchnic vessels, could produce such symptoms whenever cerebral circulation was reduced.

The cerebral complications of various surgical operations have recently been studied by Behrend and Riggs.<sup>20</sup> These authors encountered coma, convulsions, focal cerebral symptoms, hyperpyrexia, and psychic disturbances. All of their patients had low arterial blood pressure and varying degrees of shock. No thrombi, emboli, or hemorrhages were discovered in the brains which they examined.

Thomas<sup>21</sup> described a patient with postural hypotension who had recurrent attacks of transient hemiplegia during periods of low or falling arterial blood pressure. These attacks could be reproduced at will by elevating the patient on a tilting table to 75° above the horizontal. Thomas believed "this apoplexy is caused by a fleeting localized cerebral ischemia which occurs in the course of a drop in blood pressure from postural hypotension. The degree of narrowing of the lumen

from arteriosclerosis of the various cerebral vessels determines the point at which ischemia first produces symptoms.”

From the foregoing observations it is clear that a form of hemiplegia may occur in persons with cerebral arteriosclerosis when there is a precipitous or extreme fall in arterial tension. The location and extent of the arterial lesions determine the focal signs and symptoms. Their severity will be influenced by the rate of fall and the duration of the hypotension. The permanence of focal signs will depend on these factors and the resulting damage to the brain. Although spasm of cerebral vessels might produce similar effects, it does not seem likely in sclerotic vessels.

We have been able to find only one study of the cerebral symptoms of acute myocardial infarction. Kjaergaard<sup>22</sup> reported three cases in which extreme collapse, confusion, coma, epileptiform convulsions, incontinence, and restlessness were the most conspicuous symptoms. At autopsy, acute infarcts of the heart were found. Unfortunately, in two cases the brain was not examined, so that the possibility of embolism, thrombosis, or hemorrhage cannot be excluded. In the third case the patient had fallen, and autopsy revealed a traumatic hemorrhage in the occipital region. Dozzi<sup>23</sup> has studied cases in which unsuspected coronary thrombosis was discovered at autopsy when the clinical picture was that of hemiplegia. There were infarcts or hemorrhages in the brain which were sufficient to account for the neurological changes. Fetterman and Ashe<sup>24</sup> have emphasized the “cerebral debut” which occurs in certain cases of heart disease. Although their report dealt primarily with patients with subacute bacterial endocarditis, they included one case of myocardial infarction. The patient had a reaction closely simulating delirium tremens. They believed that his bizarre symptoms depended upon cerebral anoxemia. At autopsy, ischemic changes were found in the brain. Abbott and Fay<sup>25</sup> reported a case of syncope and head injury. At autopsy coronary occlusion was found, without evidence of a cerebral lesion, and presumably with normal cerebral vessels. Here it is clearly impossible to exculpate many of the usual causes of syncope.<sup>14</sup> We have reported a somewhat similar case, in which it was suspected that the shock associated with a head injury was the precipitating cause of coronary thrombosis.<sup>26</sup>

Many patients with coma are neglected until after the early clinical patterns of their disease have been obliterated. When such patients are admitted to large general hospitals, the history is often wanting or imperfect. Careful physical examination is precarious. Solomon and Aring,<sup>27</sup> in an analysis of patients admitted to the Boston City Hospital, with coma as the conspicuous presenting symptom, found that cardiac disorders were responsible for 3.5 per cent of the nonalcoholic cases. Five of seventeen were later found to have coronary thrombosis, but no report of the status of the brain and its arteries was included.

From this observation it appears that coma, rather than cerebral symptoms with localizing signs, may herald the advent of cardiac infarction. Certainly, when it appears as a sequel it may obscure the main disorder.<sup>4</sup>

#### CASE REPORTS

CASE 1.—C. R. (Unit 118100), an 83-year-old white man, was admitted to the psychiatric service April 14, 1939, because of profound disorientation. This followed a period of increasing confusion which had begun six weeks before with left-sided paralysis. No other history could be obtained.

*Physical Examination.*—The temperature was 100.5° F.; the pulse rate, 100; and the respiratory rate, 24. The patient had Cheyne-Stokes' breathing. His blood pressure measured 130/80. He was a swearing, grimacing old man, dehydrated, cyanotic, and completely disoriented. Ophthalmoscopic examination revealed some blurring of the discs and tortuous, narrow arteries. There was dullness at the base of the right lung posteriorly, and moist râles were heard at both bases. Marked peripheral arteriosclerosis was noted. The heart seemed large but could not be percussed accurately because of the emphysematous chest. The impulse was 11.5 cm. from the midline. The heart sounds were very distant, but regular. No murmurs were heard, and there was no gallop or friction rub. There was constant rhythmical twitching of the right leg. Complete flaccid paralysis of the left arm was noted. Neurological examination revealed that the biceps, triceps, radial, and patellar reflexes were 2+ on both sides (0, absent; 4+, maximal). Both ankle jerks were absent. The Babinski, Oppenheim, and Chaddock reflexes were present on the right, as was a questionable Gordon's reflex. The abdominal reflexes could not be elicited. Pain sensation was present. The neck was not stiff. Lumbar puncture revealed an initial pressure of 5 cm. of water, with normal dynamics and cerebrospinal fluid.

*Admission Laboratory Studies.*—The erythrocyte count was 5,220,000; the leucocyte count, 27,000; and the hemoglobin, 13.6 Gm. per 100 c.c. The urine was normal except for a few leucocytes in the sediment.

*Course in Hospital.*—He remained disoriented, gradually became worse, and died ten days after admission. The diagnosis was thrombosis of the left middle cerebral artery, generalized arteriosclerosis, and bronchopneumonia. (Autopsy observations in all cases are found in Table II.)

CASE 2.—J. H. (Unit 33722), a 63-year-old white man, was admitted to the receiving ward at 1:30 A.M., Jan. 2, 1935, in a state of deep coma. It was ascertained that he had been treated for heart trouble in the past. About five hours before admission he had complained of a sudden pain, and he rapidly became unconscious. There were no convulsions or twitchings. When first seen, he was in shock. There was some frothing at the mouth. All deep reflexes were hyperactive and equal bilaterally. The pupils reacted to light. Ankle clonus was present bilaterally. The cremasteric and abdominal reflexes were absent. There was no focal weakness. He died suddenly while on the way to the ward. Nothing else was recorded. The diagnosis was probable cerebral accident, with cardiac insufficiency.

CASE 3.—H. B. (Unit 78524), a 61-year-old white man, was admitted to the medical service July 15, 1937, complaining of severe dyspnea, pain in the legs, and inability to use his left arm. Three years previously he had noticed numbness and severe pain in both legs on standing. A year later he began having attacks of nonradiating retrosternal pain after exertion, which was relieved by rest and never lasted over three minutes. Dyspnea on effort began soon after the first anginal



TABLE

| CASE          | AGE<br>(YEARS) | SEX | RACE | WEIGHT<br>(GM.) | HEART  |  |  |  |   |   | MURAL   |                        |
|---------------|----------------|-----|------|-----------------|--|--|--|--|---|---|---------|------------------------|
|               |                |     |      |                 | CORONARY ARTERIES                                    |  |  |  | INFARCTS  |   |         |                        |
|               |                |     |      |                 | ARTERIO-<br>SCLEROSIS                                | L. A. D.   | CIRCUM-<br>FLEX  | RIGHT  | HEALED  | RECENT  | AURICLE | R                      |
| 1<br>U-118100 | 83             | M   | W    | 550             | ++++ with<br>ulcer-<br>ation<br>and<br>throm-<br>bus | Fresh<br>throm-<br>bus                                   | Narrow   | Narrow   | Apex of left<br>ventricle   | Apex of left<br>ventricle<br>around old<br>infarct                            | 0       | 0                      |
| 2<br>U-33722  | 63             | M   | W    | 550             | ++++   | Thrombus<br>at origin                                    | Marked<br>A. S.  | Thrombus<br>at origin                                    | Posterior and<br>basilar in<br>left ventricle   | Anterior<br>apical in<br>left ventricle<br>and septum                         | Small   | Small                  |
| 3<br>U-78524  | 61             | M   | W    | 475             | ++++ with<br>calcifica-<br>tion                      | Narrow;<br>no<br>throm-<br>bus                           | Narrow;<br>no<br>throm-<br>bus                           | Narrow;<br>no<br>throm-<br>bus                           | Anterior of<br>left ventricle   | Anterior and<br>apex of left<br>ventricle<br>around old<br>scar               | 0       | Small<br>adher-<br>ent |
| 4<br>U-67496  | 44             | M   | W    | 450             | +++  | Complete<br>occlusion                                    | Narrow   | Narrow   | Posterior and<br>basilar in<br>left ventricle<br>and septum                               | Anterior and<br>apical in<br>left ventricle                                   | 0       | 0                      |
| 5<br>U-89077  | 87             | M   | C    | 500             | ++++   | Fresh<br>throm-<br>bus                                   | Old oc-<br>clusion                                       | Narrow   | Anterior and<br>apex of left<br>ventricle;<br>posterior<br>and basal in<br>left ventricle | Anterior and<br>apical in<br>left ven-<br>tricle; large<br>around old<br>scar | 0       | 0                      |
| 6<br>U-106527 | 61             | M   | C    | 665             | +++  | Sclerotic  | Narrow   | Fresh<br>throm-<br>bus;<br>new<br>origin                 | 0   | Posterior and<br>basal in left<br>ventricle                                   | 0       | Small                  |
| 7<br>U-104989 | 53             | M   | C    | 850             | ++++   | All arter-<br>ies very<br>narrow;<br>no<br>throm-<br>bus | All arter-<br>ies very<br>narrow;<br>no<br>throm-<br>bus | All arter-<br>ies very<br>narrow;<br>no<br>throm-<br>bus | 0   | Posterior and<br>basal in left<br>ventricle                                   | 0       | 0                      |
| 8<br>U-49873  | 45             | M   | C    | 375             | ++++ with<br>much<br>calcifica-<br>tion              | Thrombus<br>at origin                                    | Narrow   | Old oc-<br>clusion                                       | Posterior and<br>basal in left<br>ventricle   | Anterior and<br>apical in<br>left ventricle                                   | 0       | 0                      |

L. A. D., Left anterior descending.

attack. For a year prior to admission he had had attacks of paroxysmal dyspnea. Nine days before admission he had a severe, prolonged attack, characterized by dyspnea, retrosternal oppression, anxiety, ashen pallor, and extreme weakness. There was no sweating, chill, or fever. At about the same time he noticed that his left arm was useless, and the next day it was painful. Later there was transient edema of this hand and both ankles. Seven days before admission he developed a cough which was productive of thick, white sputum.

*Physical Examination.*—The temperature was 97.6° F.; the heart rate, 118; the pulse rate, 80; and the respiratory rate, 32. The arterial blood pressure was 120/100. The patient was well-developed and dyspneic and had pallor and moderate cyanosis. Ophthalmoscopic examination revealed arteriovenous nicking and silver-wire arteries. There was left facial weakness. The neck veins were distended. The chest was emphysematous, and moist râles were heard at both bases posteriorly. The heart was enlarged moderately to the left, and there was a systolic murmur. The heartbeat was grossly irregular. The liver was palpable 4 fingerbreadths be-

## II

| THROMBUS  |        |                                       | PERIPH-<br>ERAL<br>INFARCTS<br>(EMBOLIC<br>PROB-<br>ABLY) | WEIGHT<br>(GM.)                                     | CEREBRAL<br>ARTERIO-<br>SCLEROSIS | THROM-<br>BUS OR<br>HEMOR-<br>RHAGE                         | BRAIN |         |  | HORIZONTAL SECTION |
|-----------|--------|---------------------------------------|---|---|-----------------------------------|---|-------|---------|--|--------------------|
| VENTRICLE |        | INFARCT                               |   |   |                                   |   | EDEMA | ATROPHY |  |                    |
| R         | L      |                                       |   |   |                                   |   |       |         |  |                    |
| Large     | Large  | Lung,<br>spleen,<br>kidneys           | 1,200   | ++++ with<br>elevated<br>calcified<br>plaques       | 0                                 | Old, small<br>in occip-<br>ital lobe                        | ++    | +       | No evidence of fresh infarct or hemorrhage   |                    |
| Large     | Large  | Right<br>kidney                       | 1,400   | ++++ es-<br>pecially<br>of basi-<br>lar ar-<br>tery | 0                                 | 0   | ±     | +       | "No striking abnormalities are noted"  |                    |
| 0         | 0      | 0                                     | 1,375   | All mod-<br>erately<br>sclerotic                    | 0                                 | 0   | ±     | 0       | "Dilated cerebral veins"; no other abnor-<br>mality noted  |                    |
| 0         | 0      | 0                                     | 1,375   | 0   | 0                                 | 0   | 0     | +       | "Horizontal section at the level of the<br>basal ganglia reveals a discrete, well-de-<br>marcated mass 5 mm. in diameter in the<br>rt. optic radiation just posterior to the<br>tail of the caudate nucleus. There are<br>gelatinous, grayish-brown areas of soften-<br>ing about 2.3 mm. in diameter in the rt.<br>frontal and left occipital lobes and in<br>the rt. insular region" |                    |
| 0         | Medium | 0                                     | 1,375   | +++ in<br>all arter-<br>ies of<br>brain             | 0                                 | Small,<br>old, in<br>tail of<br>left<br>caudate<br>nucleus  | ±     | +++     | Normal   |                    |
| 0         | Small  | Right<br>and left<br>kidneys<br>(leg) |   | ++++ in<br>all arter-<br>ies                        | 0                                 | Small, in<br>gray<br>matter<br>of right<br>parietal<br>lobe | ++    | +       | Normal   |                    |
| 0         | Medium | Right<br>kidney                       | 1,410   | Scattered<br>yellow<br>plaques                      | 0                                 | 0   | 0     | 0       | Normal   |                    |
|           |        | 0                                     | 1,425   | ++++  | 0                                 | 0   | +     | 0       | Normal   |                    |

low the costal margin, and the edge was tender. There was loss of motor power in the left wrist and fingers. Pain was produced by pressure over the left calf. All of the tendon reflexes were present. No sensory defect was elicited. Moderate edema of the ankles was present. There was some sclerosis of all palpable arteries. The pulsations in the dorsalis pedis arteries were very weak.

*Laboratory Studies.*—The erythrocyte count was 5,600,000; the leucocyte count, 7,700; and the hemoglobin, 14 Gm. per 100 c.c. The urine was acid, had a specific gravity of 1.024, and contained 2+ albumin and occasional hyaline casts. The blood Kahn reaction was negative, and the cerebrospinal fluid was normal. The electrocardiogram revealed auricular fibrillation, a ventricular rate of 80, inversion of T<sub>1</sub>, and low voltage. T<sub>2</sub> was isoelectric; T<sub>3</sub> was of low voltage; and T<sub>4</sub> was isoelectric.

*Course in Hospital.*—After the first day the blood pressure fell to 100/70, and later rose. Muscle power in the hands returned. The facial weakness cleared up, and the edema and pain in the legs disappeared. Digitalis and bed rest reduced

his pulse rate to 60, and the pulse deficit disappeared. He was discharged after three weeks with a diagnosis of generalized arteriosclerosis, coronary artery disease with auricular fibrillation, and hysterical paralysis of the left arm.

The patient was followed in the cardiac clinic from Sept. 29, 1937, until Jan. 19, 1938, and progressed very well with the help of digitalis, which was given in daily doses of 1.5 to 3.0 grains. He had some dyspnea, an occasional precordial twinge, and infrequent spells of dizziness.

*Second Admission.*—He was admitted for the second time on Feb. 10, 1938, at 9:00 P.M. That afternoon, while he was walking down the street, he suddenly fell and was found unconscious.

*Physical Examination.*—The temperature was 107.6° F.; the pulse rate, 124; and the respiratory rate, 40. The arterial blood pressure was 182/138. When first seen, he was perspiring profusely and was moderately cyanotic. Extremely stertorous breathing was observed. The head and eyes were turned to the left. The pupils did not respond to light. The left eye was tightly closed. There were clonic spasms of both legs and the left arm. He had involuntary urination and defecation. The grossly irregular heartbeat was vigorous, and the impact was felt over the entire precordium. The rhythm and rate were completely altered by each convulsion. No murmur or friction rub was detected. The liver was barely palpable. There was no peripheral edema. The tendon reflexes could not be obtained on the left. They were normal on the right, and, in addition, there were positive Babinski and Chaddock reactions on the right. The abdominal and cremasteric reflexes were absent. The patient was given 0.25 grain of morphine and 12 c.c. of paraldehyde intramuscularly. When he became quiet, he was found to have a left-sided hemiplegia of the flaccid variety.

*Laboratory Studies.*—The erythrocyte count was 3,900,000; the leucocyte count, 17,000; and the hemoglobin, 10 Gm. per 100 c.c. Lumbar puncture revealed an initial pressure of 10 cm. of water. The cerebrospinal fluid was clear, and contained 3 leucocytes and 10 erythrocytes per cubic millimeter; the sugar was 84 mg. per 100 c.c.; the protein, 40 mg. per 100 c.c.; and the chlorides (as sodium chloride), 735 mg. per 100 c.c. The Pandy test and Wassermann reaction were negative.

*Course in Hospital.*—His condition remained precarious. The temperature varied from 104° to 107.6° F. The pulse rate fell from 124 to 70 and rose again to 85. The respirations gradually increased to 50 per minute. He died sixteen hours after admission, about twenty-four hours after the seizure on the street. The clinical diagnosis was thrombosis or hemorrhage of the right lenticulostriate artery, and coronary artery disease.

CASE 4.—H. S. (Unit 67496), a white man, aged 44 years, had been seen in the psychiatric, dental, and eye clinics of the hospital prior to his admission to the medical service. April 25, 1937, in a state of deep coma. From his wife it was learned that he had had "spells" since the age of 16, and in recent years they had become increasingly severe and more frequent. They occurred chiefly at night and were characterized by complete loss of consciousness, choking sounds, frothing at the mouth, muscular rigidity, and incontinence of urine. He had suffered from some exertional dyspnea and angina of effort for the preceding two years, but there had been no edema of the ankles until a week before admission, when there was slight edema at night. There had been no paroxysmal dyspnea at night. On the morning of admission he felt weak. He suddenly complained of substernal pain, and, when his wife returned a few minutes later, he had fallen to the floor unconscious.

*Physical Examination.*—The temperature was 99.2° F.; the pulse rate, 106; and the respiratory rate, 24. The arterial tension was only 70/50. He was unconscious,

in deep shock, sweating, and had an ashen, cyanotic pallor. An intermittent cough produced brownish sputum. There were râles at the bases of the lungs. The heart was enlarged; it measured 8 cm. to the right, and 13 cm. to the left, of the mid-line. The heart sounds were faint, but no murmurs or rubs were heard. The liver was palpable 3 fingerbreadths below the costal margin. Neurological examination revealed a Babinski reaction on the left, but nothing else of consequence.

*Laboratory Studies.*—The erythrocyte count was 4,600,000; the leucocyte count, 32,200; and the hemoglobin concentration, 16 Gm. per 100 c.c. The blood Kahn reaction was negative. Blood chemical studies revealed a urea nitrogen of 30 mg. and a carbon dioxide combining power of 39 volumes per 100 c.c. Urinalysis showed 1+ sugar, with occasional leucocytes and casts in the sediment. The electrocardiogram was typical of posterior infarction.

*Course in Hospital.*—The temperature reached 101.5° F. on the second hospital day. The pulse rate gradually fell, and a systolic murmur appeared. A diagnosis of coronary occlusion was made. He was instructed to take digitalis and remain at rest in bed for six weeks.

*Second Admission.*—He was readmitted, this time on the neurological service, on June 15, 1937, in a state of deep coma. His wife stated that he had systematically disobeyed instructions, i.e., had walked about, climbed stairs, and worked. The day before admission he was apparently as well as ever. The next day, at 5:30 A.M., he had one of his usual "spells," with grunting breathing, unconsciousness, and incontinence of urine. This lasted for twenty minutes. He had another attack at 6:30 A.M., and another at 7:30 A.M., after which he was admitted. These were identical with his regular epileptic seizures, as far as his wife could tell, except that there was profuse sweating between attacks.

*Physical Examination.*—The temperature was 101.4° F.; the pulse rate, 120; and the respiratory rate, 42. The arterial blood pressure was 100/80. The patient was in deep coma, cyanotic, and sweating, with rapid, shallow breathing. There were slight abrasions on the head about the right occipital region. A few fine râles were heard at the base of the right lung. The heart was enlarged, and a rough systolic murmur was heard. The heart sounds were of very poor quality. The liver was barely palpable. The neurological examination showed nothing remarkable.

*Course in Hospital.*—He rapidly developed bilateral ankle clonus and positive Babinski and Chaddock signs. He began to turn his face regularly to the left. He had generalized rigidity, especially on the left. Signs of pneumonia of the right lower lobe developed, and a Type XIII pneumococcus was recovered from the sputum. His temperature and pulse rate rose rapidly. It was believed by members of the house staff and visiting staff that the clinical manifestations could best be explained as postepileptic exhaustion complicated by bronchopneumonia. The patient died on the third hospital day.

CASE 5.—L. S. (Unit 89077), an 87-year-old colored man, was admitted to the neurological service March 2, 1938, in a comatose condition. The history, obtained from a friend, indicated that he had been well until a week before admission, when he developed a "toothache" and a headache in the left temporal region. He was aroused with difficulty on the morning of admission and said he felt queer. He was still confused in the afternoon, and shortly before he was brought to the hospital he became aphasic. Twitching of the right side of the face, right arm, and right leg was observed. No cardiac symptoms had been noted.

*Physical Examination.*—The temperature was 100.8° F.; the heart rate, 110; the pulse rate, 66; and the respiratory rate, 30. The blood pressure was 160/100. The patient was comatose, and his entire right side was involved in rapidly repeated

involuntary twitching movements. The pupils were irregular, the right more so than the left; both reacted sluggishly to light. The cyanotic tongue had been bitten recently, exhibited twitching, and was deviated to the left. The neck veins were distended. Râles were heard at the bases of the lungs. The heart was enlarged. The heartbeat was grossly irregular, and the sounds were of fair quality. Marked sclerosis of the superficial arteries was noted. There was no edema. Neurological examination revealed a complete right hemiplegia when he was not twitching. The pectoral, biceps, and triceps reflexes were equal. The knee and ankle jerks were present on the left, but absent on the right. There was a questionable Babinski and Rossolimo reflex on the right.

*Laboratory Studies.*—The erythrocyte count was 4,200,000; the leucocyte count, 9,500; and the hemoglobin, 14 Gm. per 100 c.c. The urine was alkaline, of a specific gravity of 1.025. It contained 3+ albumin and a few leucocytes and granular casts. The blood Kahn reaction was negative. Blood chemical studies revealed a urea nitrogen of 32 mg. and a carbon dioxide combining power of 44 volumes per 100 c.c. The cerebrospinal fluid was clear, with an initial pressure of 12 cm. of water; there were 10 leucocytes per cubic millimeter. The protein was 48 mg. per 100 c.c.; the sugar, 65 mg. per 100 c.c.; and the chlorides, 682 mg. per 100 c.c. The electrocardiogram showed left axis deviation. The QRS complexes were slurred in Leads II and III. T<sub>1</sub> was inverted; S-T<sub>1</sub>, elevated; and S-T<sub>3</sub>, depressed. There were extrasystoles from three foci in the ventricle.

*Course in Hospital.*—The pulmonary edema increased, and the patient died on the third hospital day, in spite of digitalization and other treatment. The blood pressure did not fall below 140/100 until just before death. The clinical diagnoses were cerebral hemorrhage into the left internal capsule, with right hemiplegia, and arteriosclerosis of the coronary arteries. One observer suggested the possibility of a subdural hematoma.

CASE 6.—R. T. (Unit 106527), a 61-year-old colored man, was admitted to the surgical service Oct. 31, 1938, with a complaint of pain in the left leg and foot. The past history was not accurate, but he had had exertional dyspnea for several years, with intermittent claudication and occasional edema of the ankles which disappeared at night. For five years he had had frequent attacks of precordial pain which were precipitated by exertion or emotion. There had been attacks of dizziness and "spots before the eyes." Three weeks before admission he had had a right-sided hemiplegia, with aphasia, which lasted only a few hours. Two weeks before admission he had a syncopal attack, after which his mind had been cloudy. One week before admission he had "blind staggers," with vague epigastric pain, for which he had consulted his family physician. The day before admission, while walking, he had a sudden, severe pain in his foot and the inner portion of his left leg.

*Physical Examination.*—The temperature was 97.2° F.; the pulse rate, 92; and the arterial blood pressure, 170/110. He was moderately obese and was apprehensive at times. He was comfortable lying flat in bed, but his neck veins were engorged. The heart was enlarged to the left. The sounds were of poor quality, and there were numerous extrasystoles. No murmurs were heard. Moist râles were detected at the bases of the lungs. The left leg was swollen and cold, and no pulse was felt below the femoral artery. The reflexes were normal.

*Admission Laboratory Studies.*—The erythrocyte count was 4,300,000, and the leucocyte count, 15,000. The urine was acid, with a specific gravity of 1.017; it contained 4+ albumin, leucocytes, and granular casts. Lumbar puncture revealed a normal cerebrospinal fluid under a pressure of 22.5 cm. of water. The blood urea nitrogen was 29 mg. per 100 c.c., but fell to 14 on the third day. On the seventh hospital day the carbon dioxide combining power was 54 volumes per 100 c.c.

*Course in Hospital.*—The leg improved somewhat with passive vascular exercise. On the third night after admission the patient became irrational, got out of bed, and wandered around. He was completely disoriented, and there was a sudden rise in temperature to 102° F.; the pulse rate reached 110. He expressed a fear of death. He was slowly digitalized, but gradually grew worse. Eight days after admission a medical consultant saw him and noted profuse sweating, coma, deep, stertorous breathing, and pulmonary edema. The tongue deviated to the right. The right arm was flaccid. The abdominal and cremasteric reflexes and the knee jerks were absent. There were no reactions to plantar stimulation and little reaction to painful stimuli. It was suggested that the patient had a cerebral hemorrhage. Another lumbar puncture showed that the spinal fluid was still normal. The electrocardiogram revealed a rate of 80, with sinus rhythm and left axis deviation. The QRS complexes were slurred and of low voltage in all leads. The P-R interval was 0.22 to 0.24 second. T<sub>1</sub> and T<sub>4</sub> were inverted. T<sub>2</sub> was isoelectric, and T<sub>3</sub> showed low voltage. He developed Cheyne-Stokes respiration. The temperature rose to 106.8° F., and the patient died on the ninth hospital day. The clinical diagnosis was probable cerebral accident. One observer suggested the possibility of coronary occlusion.

CASE 7.—G. C. (Unit 104989), a 53-year-old colored man, was admitted to the medical service Oct. 19, 1938, with the complaint of being "choked up and stopped up in the head." The family history revealed that his father had died of "acute indigestion" and his mother of heart trouble, and, of six dead siblings, three died of heart trouble of an unspecified variety. At the age of 18 years he had had typhoid fever which was followed by enlargement of the right leg. This had been treated seventeen years later by excision of varicose veins. He had had a chancre sixteen years before. At times he had experienced sharp epigastric pains when he had "gas on the stomach." He had had attacks of dizziness and headache for approximately one year. His present illness began four months before admission with a severe attack of asthma, which lasted thirty-six hours and left him with a chronic cough and occasional attacks of paroxysmal dyspnea. He stopped work until a month before admission, when he took a job as hod carrier and worked for a week. One day while at work he was seized with a sudden, severe attack of dyspnea and weakness. There was no pain then or later. He had increasing dyspnea and orthopnea, with edema of his good and bad leg. He was admitted because of the increasing dyspnea.

*Physical Examination.*—On admission the temperature was 99.6° F.; the pulse rate, 116; and the respiratory rate, 36. The arterial blood pressure was 170/134. He was a severely dyspneic colored man with an anxious expression, and was propped up in bed. At times he coughed up frothy sputum. The neck veins were engorged. Moist râles were heard throughout the chest. The heart was markedly enlarged, with dullness 14 cm. to the left of the midline in the sixth intercostal space and 4 cm. to the right in the fourth intercostal space. There was a suggestion of gallop rhythm at the apex, and the aortic second sound was very loud. The liver extended 4 fingerbreadths below the costal margin, and was tender. The right leg was edematous and was the seat of extreme fibrosis; there was an ulcer on the shin which measured 3 by 6 cm. The left leg was swollen also, but only to half the size of the right. Neurological examination was negative.

*Laboratory Studies.*—The erythrocyte count was 3,500,000; the leucocyte count, 6,800; and the hemoglobin, 10.7 Gm. per 100 c.c. The urine was acid; its specific gravity was 1.038; it contained 2+ albumin and a few leucocytes and erythrocytes; many hyaline and granular casts were found in the centrifuged specimen. The blood Kahn reaction was negative. The blood urea nitrogen was 23 mg. per 100 c.c. The clear cerebrospinal fluid had an initial pressure of 23 cm. of water; there

were 2 leucocytes per cubic millimeter, the protein was 16 mg. per 100 c.c., and both the Pandy test and Wassermann reactions were negative.

*Course in Hospital.*—He was treated with morphine and aminophylline and was digitalized rapidly. His pulse rate fell to 100; his respirations, to 10. The temperature remained the same. Early in the morning of the second hospital day he suddenly became unconscious, had Cheyne-Stokes respiration, and lost all of his reflexes except a slow corneal response. The blood pressure was 74/50. There were no signs of pyramidal tract disease. He died three hours after the onset of the unconsciousness. The clinical diagnosis was cerebral hemorrhage, in addition to the admission diagnosis of hypertension and arteriosclerotic coronary artery disease, with severe cardiac failure, and elephantiasis and ulceration of the right leg.

CASE 8.—R. F. (Unit 49873), a 45-year-old colored man, was admitted to the surgical service Dec. 30, 1935, with frostbite of both hands which he incurred when shoveling snow on Christmas Eve. There was nothing in the history to suggest cardiac disability of any kind.

*Examination.*—The temperature was 100.6° F.; the pulse rate, 106; and the arterial blood pressure, 130/90. The heart was normal in all respects. The liver was barely palpable, but not tender. No edema was present. First degree frostbite of both hands was observed. A single urine specimen was negative. The blood Kahn reaction was strongly positive (3+).

*Course in Hospital.*—The patient was treated with passive vascular exercise for twenty minutes a day, twelve times during the first three weeks in the hospital. There was some sloughing of the fingers, which were débrided from time to time. He was progressing well when he suddenly became severely nauseated early in the morning of the thirty-sixth hospital day, and complained that he had slept poorly. He was given peppermint water and, at 9:00 A.M., vomited several times. At noon he felt better and was walking about the ward, when he suddenly fell across a bed and began to have stertorous respiration. Within about one minute his pulse and heartbeat were imperceptible, and his respirations grew irregular. He died seven minutes after the syncopal attack began. His jaws were clamped tightly together. No other neurological abnormalities were found. Intracardiac injections of adrenalin and caffeine did not revive him. It was believed that he had a cerebral hemorrhage, thrombosis, or coronary occlusion.

#### COMMENT

These cases revealed a variety of cerebral symptoms in association with acute cardiac infarction. Hemiplegia, coma, syncope and shock, epileptic convulsions, vomiting, and mental disturbances, with confusion and delirium, were some of the manifestations. The physiologic factors concerned with the various types of symptoms are obscure, but it is reasonable to suppose that cerebral arteriosclerosis, together with reduced blood flow, was the major localizing factor. Each case must be individualized in order to understand the mechanism concerned.

Certain general observations are justified. The diagnosis of infarction of the heart is very difficult from physical examination alone. When the sensorium is clouded, and no history is available, it may be overlooked. This is particularly true when neurological signs point to a localized lesion in the brain. These cases indicate that marked neurological disturbances may occur in infarction of the heart, without any acute or rapidly progressing vascular lesion in the brain. The reason

probably is that relative ischemia of the brain occurs because the heart is hypodynamic. In an area in which the caliber of the arteries is fixed, blood flow is influenced by arterial pressure and the rate of the circulation. When the pressure falls, the flow is reduced. From the literature which has been cited, it is clear that a fall in arterial tension may produce focal neurological signs in the presence of arteriosclerosis of the cerebral vessels. It is assumed that the location of resulting neurological disturbances is determined by the distribution of the cerebral vascular constrictions.

It is possible that reflexes from the heart to the brain may produce similar cerebral manifestations. This is true of carotid sinus syncope.<sup>14</sup> Nothing is known of the exact mechanism in such cases, but one suspects that changes in the caliber of the cerebral vessels are concerned.

In the instances in which pulmonary congestion is marked, anoxemia is added to the damage produced by the focal ischemia of the brain. Ischemia, when the blood is well oxygenated, is naturally less deleterious than when blood is poorly oxygenated.

It may be of importance that all of our patients were men. More than the expected proportion were colored. Except in Case 4, all showed severe arteriosclerosis, particularly in the medium-sized arteries.

We wish to stress, finally, the tendency of each patient who had more than one attack to exhibit similar manifestations in each. This emphasizes an important, though often neglected, point. Disease of whatever kind is superimposed upon the substratum of the patient. His physical makeup, if it deviates far from the norm, will reflect disease in an aberrant form.

#### SUMMARY AND CONCLUSIONS

Clinical and morphologic data are presented in eight cases in which there were symptoms of acute cerebral disease associated with infarction of the heart. No clinical diagnosis of heart disease was made because the bizarre central nervous system manifestations obscured the picture.

The most likely cause of this unusual syndrome is that a fall in arterial blood pressure reduces cerebral circulation. When the cerebral vessels are narrowed and rigid from sclerosis, the resulting ischemia gives rise to focal signs. Congestive failure, with its attendant anoxemia, may increase the local anoxia of the brain.

In an epileptic patient, cardiac infarction was associated with a series of convulsions which were similar to the ordinary seizures.

These cases show that there are aberrant forms of a well-recognized syndrome. The abnormal physical substratum of the patient distorts the clinical picture by producing complications which camouflage the main disorder.



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# QUANTITATIVE MEASUREMENT OF REACTIVE HYPEREMIA IN HUMAN SKIN

## INDIVIDUAL AND SEASONAL VARIATIONS

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THE immediate object of this study was to establish a simple, reliable technique for the estimation of functional changes in the condition of the smallest blood vessels in human skin. This paper is concerned with the second of two such methods. The first of these, which was reported elsewhere,<sup>1</sup> depends largely upon the contractile sensitivity of the smallest blood vessels of the skin to graded mechanical stimulation; the present method measures the capacity of these vessels to respond by reactive hyperemia to a given period of local ischemia. The fact that the amplitude and duration of the response are dependent largely upon the duration of circulatory stasis was established by Lewis<sup>2</sup> and confirmed by others.<sup>3-5</sup> It appeared, therefore, that a procedure could be devised whereby local ischemia might be maintained for a time just sufficient to elicit a given degree of reactive hyperemia. This would then serve as a measure of the reactive capability of the smallest blood vessels in the skin. The present paper, in recording such a method, notes certain seasonal, individual, and physiologic factors which affect this property of the cutaneous blood vessels and tissues.

The uses of such a measure of skin function are several. Its chief value should be to provide a means of estimating how disease, physiologic processes, and therapeutic agents affect the capacity of the skin to yield substances which give rise to reactive hyperemia.

## METHODS AND PROCEDURES

This method for measurement of reactive hyperemia in the skin depends upon a suitable instrument and an adequate procedure for its application.

An instrument was devised to enable one to apply weights with deftness and accuracy to the forearm of a subject for varying lengths of time. As can be seen in Fig. 1, this aim was attained by mounting three pans on levers, made of Brown and Sharp 9 gauge wire, which limit their motion to an arc in a vertical plane perpendicular to the axis of the forearm. The lifting and lowering lever is made

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of the same wire and is arranged with enough mechanical advantage so that the pans may be lowered slowly and gently upon the arm.

The construction details are simple. The top plate (Fig. 1) is of heavy-gauge, galvanized iron, 11 by 15 inches in size, with a rectangular, 1.75 by 6 inch cutout at one end. The lower portion is made of 0.75 inch wood stock and is about 5 inches deep. It was found advisable to cover the under side of the region bordering the cutout in the plate with velvet or felt in order to forestall any possible blood vessel reaction caused by contact of cold metal with the skin. The weight holders, or pans, are the lower portions of 1 oz. salve tins. Although any substance might conceivably be used for the actual application portion of the pans, we found in practice that the following arrangement was the most efficient. A strip of rubber, 0.5 by 0.5 by 10.0 cm. in size, is shaped into a circle and cemented in the center of a disc of metal 4.5 cm. in diameter. This disc, in turn, is cemented to a layer of sponge rubber, and, finally, the whole is applied to the bottom of the pans. The discs are curved slightly to fit the contour of the arm. It is also desirable to smooth with fine emery paper the sharp edges from the rubber applicator rings in order to prevent cutting into the skin. This would falsify the end point of the reaction, as noted below.

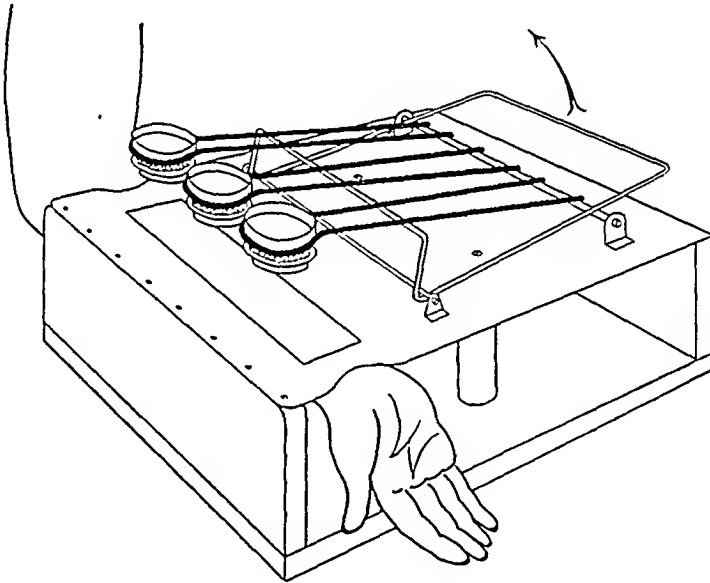


Fig. 1.—Diagram of instrument with which three areas of reactive hyperemia may be made simultaneously upon the inner aspect of the arm. By ascertaining the minimal length of time necessary to just induce rings of uniform color, size, and sharpness, one may obtain a measure of reactive hyperemia. (See Fig. 2 and text for discussion.)

Thus it is seen that the whole arrangement is designed to provide a maximum of application despite variations in arm contour and unavoidable position differences of different arms. The use of equal weights (500 Gm.) in the three pans and their application over three areas of equal size and shape offer ample opportunity for comparison of the several responses. This was found to be desirable. The actual application surface of the rubber rings amounts to approximately 5 sq. cm. (0.5 by 10 cm.). Thus the load is 100 Gm. per square centimeter.

*Procedure.*—Observations are best made in a quiet room, free from drafts, and at a room temperature of about 70° to 75° F. The subject is seated in a comfortable position, with the arm inserted in the supine position. It is supported snugly, but not tightly, in place by a rubber wedge. The subject should rest for several minutes.

The field is illuminated by two blue (photographic), 100-watt mazda lamps, with reflectors, placed at a distance of about two feet from the arm. These are focused to one side of the cutout on the instrument.

As the weights are applied quickly to the skin, a stop watch is started. The weights are left in place for a suitable length of time (see below), then lifted off swiftly, and the ischemic areas watched closely for the color pattern, its course of development, and duration. After the areas are well cleared, the position of the arm is shifted slightly, and the effect of another period of ischemia is ascertained until the threshold level is obtained. The threshold is ascertained in the following manner.

*The Threshold Response.*—Judgment as to what constitutes the end point in any one observation depends upon the color quality, the texture, the discreteness of the edges, and the width of the rings which result from stimulation for graded lengths of time, as described above. When the period of ischemia ("stimulation-time") is relatively short, release is followed by blanching of the area of application. In two to three seconds the blanched area begins to fill in with a purplish hue which builds to a maximum intensity in twelve to eighteen seconds. At this time, careful observation reveals that the texture is mottled, the edges uneven, and the width somewhat less than 0.5 cm. The rings may be incomplete. This is a subthreshold response (Fig. 2C). When the stimulation time is increased, a point is reached at which the color becomes bright red, the rings are of even texture and have discrete edges, and the width approximates 0.5 cm., i.e., the exact size of the application area. This constitutes a threshold response (Fig. 2D). Relatively high stimulation times (over the threshold) cause very bright red rings which are larger than 0.5 cm. in width and are surrounded by an arteriolar flare (Fig. 2B). Various degrees of responses may, of course, be obtained, depending on the stimulation time, but the observer, by trial and error and by adopting a standard routine, soon learns to pick out the threshold with an accuracy of two to five seconds. At the threshold, the time that is taken for the rings to fade to the hue of the surrounding skin is noted. This constitutes the "clearing time" and normally equals or exceeds the stimulation time.

When the weight loading is less than 15 Gm. per square centimeter, relatively long stimulation times (five to ten minutes) produce only cyanotic, narrow rings in every instance (Fig. 2A). By experiment it was found that a loading of at least 20 Gm. per square centimeter had to be used before the red flush of reactive hyperemia could be obtained with short stimulation times. As the loading is increased up to 100 Gm. per square centimeter, not only is the resulting reactive hyperemia more intense, but the threshold is shortened.

It is generally agreed that capillary pressure extends, on an average, from 12 mm. of mercury in the venous end to 32 mm. of mercury in the arterial end of the capillary loop (in the finger). Simple calculation shows that this corresponds to a weight loading of roughly 16 Gm. per square centimeter for the former, and 44 Gm. per square centimeter for the latter, and that this is just sufficient to cause ischemia of the vessels, not counting the resistance of the tissues themselves. Since weight loadings of 15 Gm. or less do not cause reactive hyperemia, it must be inferred that complete occlusion of at least the venous end of the capillary loop is requisite for the threshold response. Furthermore, the increasing intensity of the reactive hyperemia and the decrease in the threshold with weight loadings which exceed purely occlusive pressures suggest that there is an added factor of tissue injury. This agrees with the observations of Lewis<sup>2</sup> and is important in the study of the results and discussion which follow.

## RESULTS

*Individual Responses.*—In July, 1940, at the outset of this study, the minimal length of time necessary to elicit the liminal response (Fig. 2D) ranged from four seconds in one subject to eleven seconds in another. The subliminal response (Fig. 2C) was read to within two seconds in each case. Repeated observations on five subjects at this time

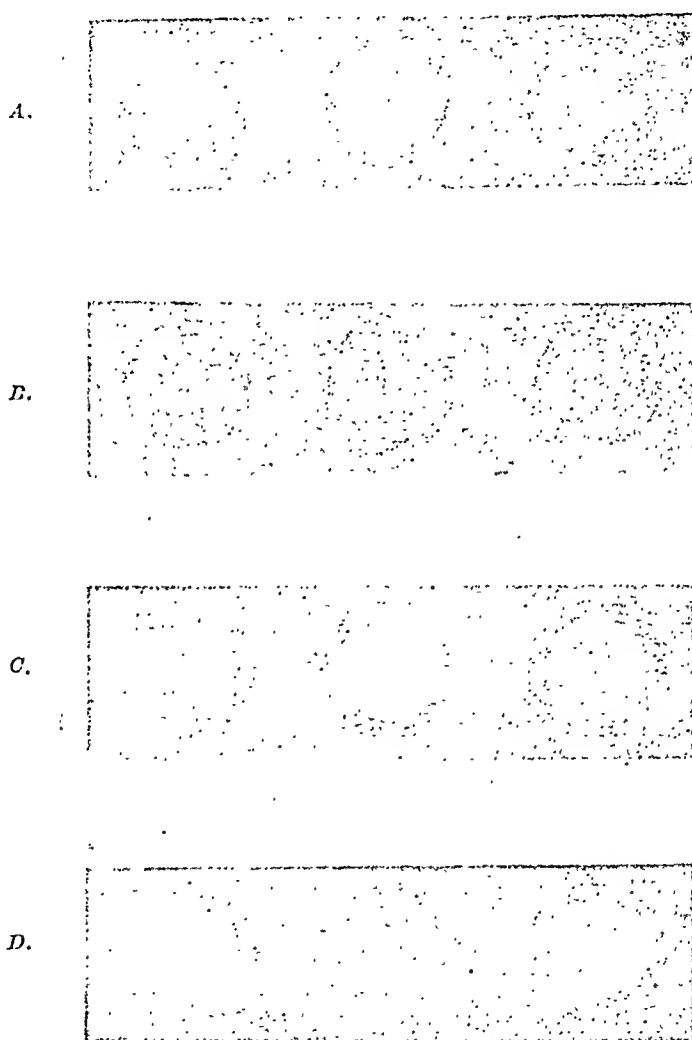


Fig. 2.—Drawings of the types of response which may be elicited with the device shown in Fig. 1. A, Cyanotic rings; B, maximal response with reflex flare; C, just subliminal response (diffuse edges, uneven width, and mottled appearance); D, threshold response, induced by application of the weights for a time just long enough to give rise to rings of uniform color and size, with discrete edges.

gave values which fell within this range. On any given day, the threshold response remained constant at this season of the year. It was unaffected by ordinary degrees of activity and not modified in any regular way by meals. This was tested by examining threshold levels on subjects with a normal caloric intake and those with very low or no caloric intake. The positions of these subjects were then

reversed and the thresholds again examined. No significant change was noted. With regard to exercise, no appreciable difference was observed in the threshold level of reactive hyperemia in the skin immediately before exercise and immediately afterward (stepping on and off a stool 100 times within a few minutes). Similarly, after the patient had rested, recumbent, for an hour, the threshold was found to be unchanged. Accordingly, moderate changes in body metabolism exert no immediate influence upon the capacity of the cutaneous vessels to give the reactive hyperemia response.

Observations were also made on the possible influence of psychic factors.<sup>6</sup> Subjects who presented evidence of emotional instability, as noted from time to time by the student health office, were studied, and in other subjects the hyperemia threshold response was examined before and after acute psychic stimulation. Our conclusions were that, although prolonged psychic upsets might alter the threshold even during the course of its determination, acute psychic trauma did not have a discernible effect. Accordingly, all subjects who were suspected of emotional instability were eliminated from the series reported in this paper.<sup>6</sup>

*Seasonal Variations.*—As the summer ended and fall advanced, a gradual and progressive change was found in both the stimulation time and the clearing time of the response. By September, the threshold was thirty to thirty-four seconds in duration, and the clearing time averaged about forty seconds. By December, these values were more than doubled (Fig. 3).

The change in the time course of the reactive hyperemia response was not the result of conditioning of either the subjects or their skin to the process of repeated stimulation employed in this study. This is attested by the fact that, as the threshold values increased progressively with the season in the initial group, data obtained from new subjects who were recruited throughout the fall and winter showed similarly high threshold and clearing time values. Specific instances of this in a few cases are summarized in Table I.

Throughout the more than eleven months spanned by this study, over 500 observations were made on more than 100 subjects. This group was comprised of medical students (male and female), laboratory workers, and members of the teaching staff. Still others, whose responses were comparable in every way to those of the main group of subjects, were two male castrates and two castrated subjects. The composite curve of the average weekly thresholds and clearing times is shown in Fig. 3, along with data on external weather conditions compiled from the official weather reports of the New York area, and on the mean temperature and relative humidity which prevail in the laboratory throughout the year.

<sup>6</sup>For the sake of brevity, detailed data on this phase of the problem have been omitted.

The seasonal character of the data is unmistakable. The periods of change seem to coincide inversely with two conditions, namely, external temperature and indoor humidity. Despite the fact that most of our subjects were exposed to outside weather for only two hours a day, or less, throughout most of the year, it seems probable that the seasonal variation in reactive hyperemia is affected by external temperature

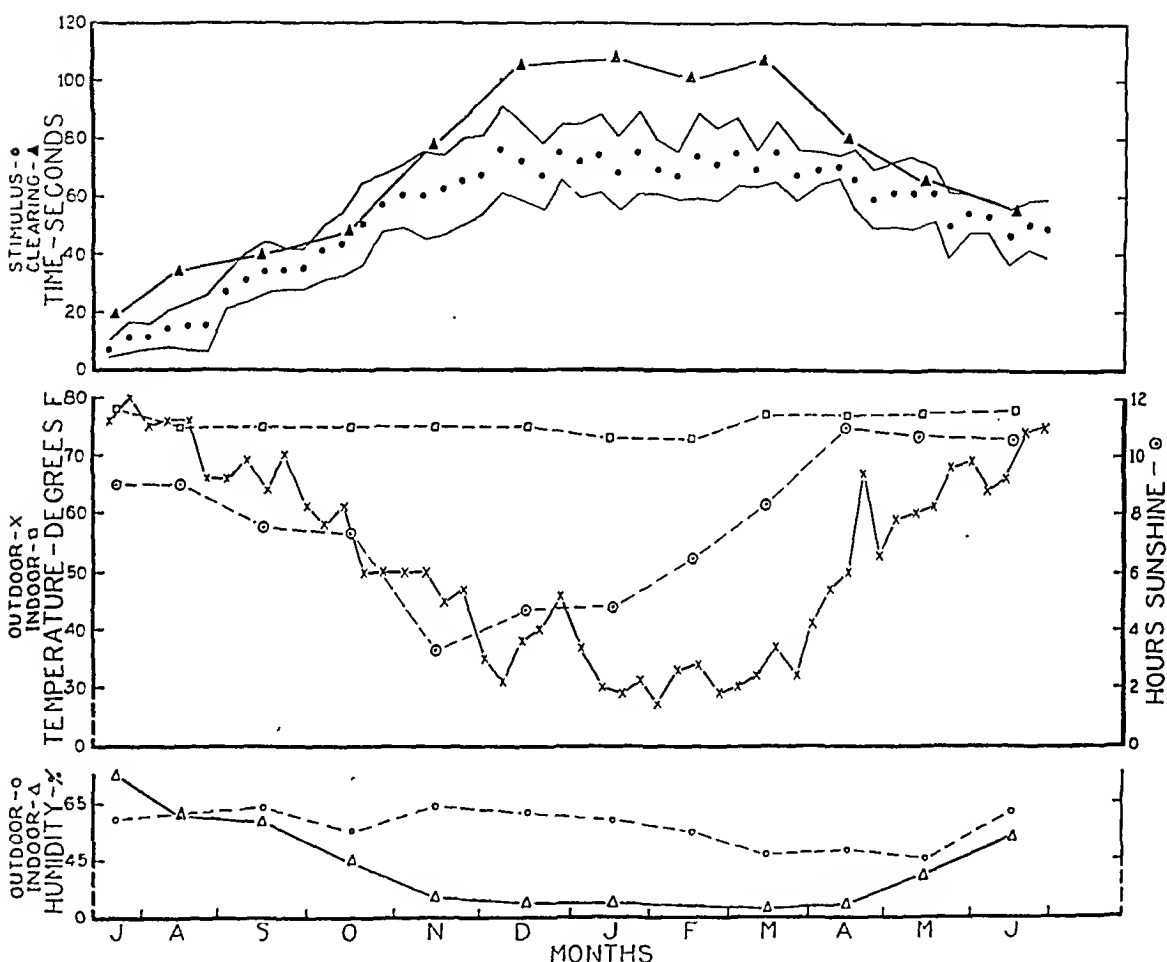


Fig. 3.—Curve of the average weekly threshold response of reactive hyperemia (dots), and clearing times for the response (triangles), from July, 1940, through June, 1941. Range of standard deviation, light lines. Data on external weather conditions were compiled from official weather reports and indoor laboratory conditions from day to day. More than 500 observations were made on over 100 subjects. Weekly averages contain no more than one reading from any single subject.

rather than indoor humidity, for heat loss and body adjustments to temperature are affected by dry-bulb, rather than wet-bulb, readings.<sup>7, 8</sup> The clearing times show a seasonal variation, along with the stimulus times. The average weekly curves show that the two phenomena do not parallel each other, however. The stimulus time lengthened appreciably before the clearing time, but, in the spring, the latter underwent a change long before the former. The clearing time, as will be seen

in Fig. 3, correlates more closely with the change in external temperature than does the stimulus time. Since, as will be shown below, the clearing time is affected to a large degree by the rate of blood flow through the skin, and this, in turn, is influenced to a large degree by the temperature of the environment,<sup>9,10</sup> the foregoing correlation is consonant with known facts.

TABLE I

DATA SHOWING THE SIMILARITY IN THRESHOLD VALUES OF REACTIVE HYPEREMIA BETWEEN FIRST OBSERVATIONS ON NEW SUBJECTS AND ON TWO WHO WERE USED FROM OUTSET

| DATE    | SUBJECT A        |                      | SUBJECT B        |                      | NEW SUBJECTS, FIRST READING |                  |                      |
|---------|------------------|----------------------|------------------|----------------------|-----------------------------|------------------|----------------------|
|         | THRESHOLD (SEC.) | CLEARING TIME (SEC.) | THRESHOLD (SEC.) | CLEARING TIME (SEC.) | SUBJECT                     | THRESHOLD (SEC.) | CLEARING TIME (SEC.) |
| July 25 | 3-6              | 17                   |                  |                      | H                           | 8-10             | 27                   |
| 30      | 6-8              | 19                   | 6-8              | 27                   |                             |                  |                      |
| Aug. 1  |                  |                      | 8-10             | 24                   | C                           | 8                | 28                   |
| 8       |                  |                      | 12-14            | 32                   | F                           | 10-12            | 27                   |
| Sept. 3 | 25-28            | 47                   | 28-30            | 39                   | G                           | 22-25            | 35                   |
| 9       | 30-33            | 39                   |                  |                      |                             |                  |                      |
| 19      | 33-35            | 38                   |                  |                      |                             |                  |                      |
| 21      |                  |                      | 24-26            | 38                   | E                           | 30-33            | 33                   |
| 24      | 20-23            | 39                   |                  |                      |                             |                  |                      |
| 26      |                  |                      | 43-45            | 55                   | D                           | 28-30            | 36                   |
| Oct. 3  | 30               | 35                   |                  |                      | I                           | 45-48            | 39                   |
| 8       |                  |                      |                  |                      | J                           | 43-45            | 51                   |
| 14      | 43-45            | 46                   |                  |                      | K                           | 45-50            | 61                   |
| 23      | 38-40            | 41                   |                  |                      |                             |                  |                      |

*The Response During Circulatory Stasis.*—The effect of complete circulatory stasis upon the threshold and clearing times was studied. This was done in order to ascertain to what extent the response depends upon a continuous flow of blood. The results of such experiments are summarized in Fig. 4.

Occlusion of the circulation for five to fifteen minutes was found repeatedly, and at different times of the year, to have no effect on the threshold time. As long as the circulation was occluded, however, the colored rings failed to clear. Under the conditions of these experiments, therefore, the threshold is not modified by cessation of blood flow, with all that that entails, but the disappearance of reactive hyperemia requires the circulation of blood. This agrees with the qualitative observations of Lewis,<sup>2</sup> but only in part with those of Goldschmidt,<sup>11</sup> who observed that reactive hyperemia continues for a long time when the arm is in normal atmospheric air but disappears rapidly (in the skin) when the arm is surrounded by pure oxygen.

*The Response After Release From Stasis, i.e., During Reactive Hyperemia.*—The thresholds and clearing times were studied during reactive hyperemia, after circulatory stasis. In contrast to the conditions described above (in which the response was studied during stasis), the



threshold is appreciably increased when the test is made during the period of increased blood flow (Fig. 4*B*). In view of the fact that cessation of blood flow has no effect upon the threshold when it is measured during stasis, this increase in the threshold with increased blood flow could be explained by more rapid dissipation of a vasodilating substance. By the same token, the elevated threshold times would then result from the necessity for greater production of a dilating substance, in order to offset an increased rate of removal.

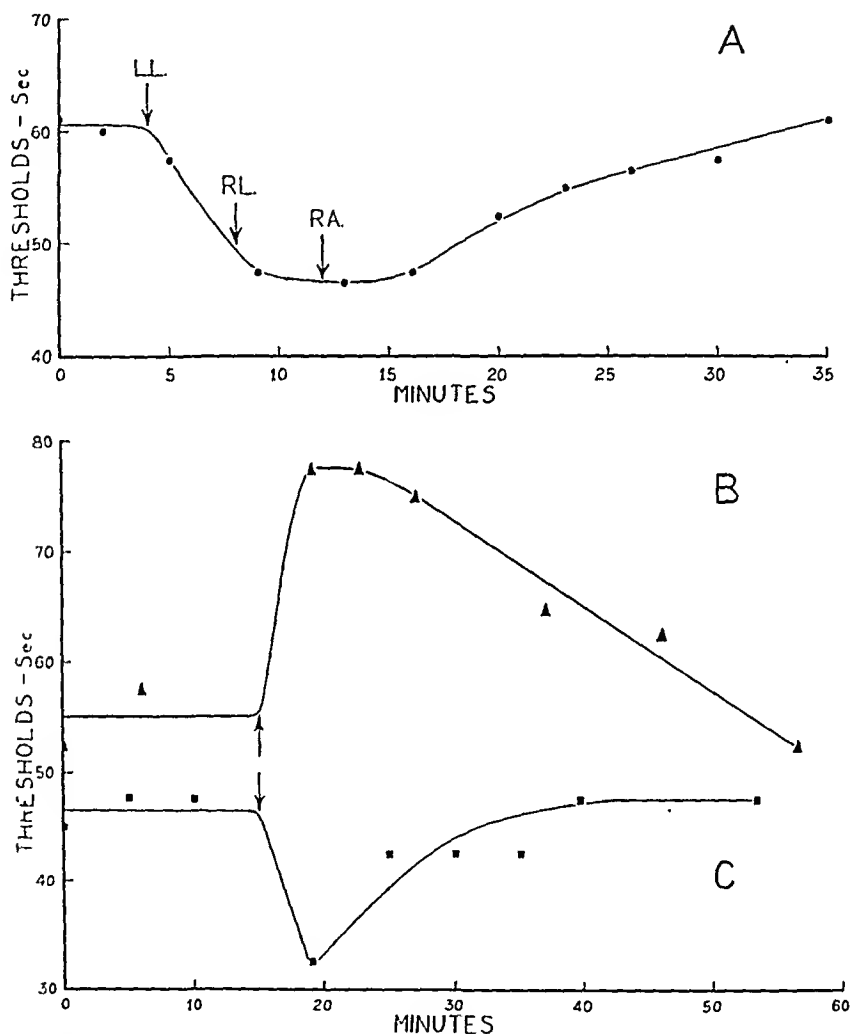


Fig. 4.—Effects of circulatory stasis on threshold responses. *Top*, the effect in the left arm after release of stasis after five minutes in the left leg (L.L.), ten minutes in the right leg (R.L.), and fifteen minutes in the right arm (R.A.). This shows the presence throughout the body of the products of stasis, without effect on heart rate or blood pressure. *Middle*, the effect on threshold during period of reactive hyperemia after release from stasis in the same arm (i.e., with augmented blood flow). *Bottom*, the effect on threshold after release from stasis (same arm), but with the circulation momentarily occluded during the tests. (See text for discussion.)

The foregoing inference is supported by another type of experiment. The circulation was temporarily occluded during reactive hyperemia, at the time the test reading was being made. Significantly, the threshold was found to be transiently lower than the control, or normal,

threshold (Fig. 4C). The higher threshold in the presence of an unrestricted, augmented flow of blood through the skin (Fig. 4B) is the result, therefore, of the requirement for more dilating substance to make up for its rapid removal. The lowering of the threshold during the initial phase of the period of reactive hyperemia in this experiment needs explanation, inasmuch as stasis alone does not alter the threshold. This explanation was found in the following experiments.

In a recumbent subject, the circulation was occluded at both knees and above the right elbow. The stimulus and clearing times were measured at four- or five-minute intervals in the left forearm. At the end of five minutes' occlusion, the circulation was released in the left leg; after ten minutes, it was released in the right leg, and after fifteen minutes, the circulation of the right arm was re-established. Although there was no change in heart rate, or systolic and diastolic blood pressures,<sup>5</sup> a marked *decrease* in the threshold for reactive hyperemia was encountered in the left arm. After release from circulatory stasis, therefore, a substance is presumably washed away during reactive hyperemia which affects the threshold for reactive hyperemia in a remote part of the body (Fig. 4A). It is therefore clear that the lower threshold in an arm with reactive hyperemia (and with the circulation momentarily occluded, as in Fig. 4C) is attributable to the presence in the affected tissues of some dilating substance or substances. Hence a less than normal additional stimulus suffices to evoke the reactive hyperemia response. The evidence that there is a washing away of the vasodilating substance during hyperemia is therefore threefold: (1) With stasis alone the stimulus time is unaffected, but the rings do not clear; (2) with increased blood flow, greater stimulation is required to evoke the response; and (3) the effect of this dilating substance has been shown upon washing away on remote tissues which are not directly involved in the production of the substance.

The reason why the threshold during simple circulatory stasis without previous hyperemia is unchanged must remain for the present without an explanation based on facts. It appears paradoxical that, during occlusion of the circulation, a substance is produced which will alter the threshold *after* the circulation is re-established, but does not affect the threshold unless this condition is fulfilled. The view advanced by Lewis<sup>2</sup> is consonant with our observations. This author postulates that the dilating substance is produced intracellularly and that it cannot be brought into contact with the blood vessels unless the flow of blood is re-established. Likewise in agreement with Lewis is our observation that tissue trauma (in the present case, application of the weights causing ischemia) will effect release of some of the dilating material and thus permit the local appearance of reactive hyperemia in an arm which is the seat of circulatory stasis. In summary, these considerations show that the clearing time of the response is affected by certain alterations

in blood flow through the skin and that the stimulus time is thus influenced *indirectly* by the rate of removal of the dilating substances produced during the period of ischemia. This conclusion seems at variance with the seasonal curve, however, for blood flow in the skin increases in warm weather<sup>9, 10</sup> and so might contribute to the shorter clearing time which is present in the summer months, but it fails to account for the similarly shortened stimulus time in the summer. This, it appears, must be accounted for by seasonal fluctuations in the capacity of the tissues to produce dilating substances, or by altered sensitivity of the blood vessels, or both.

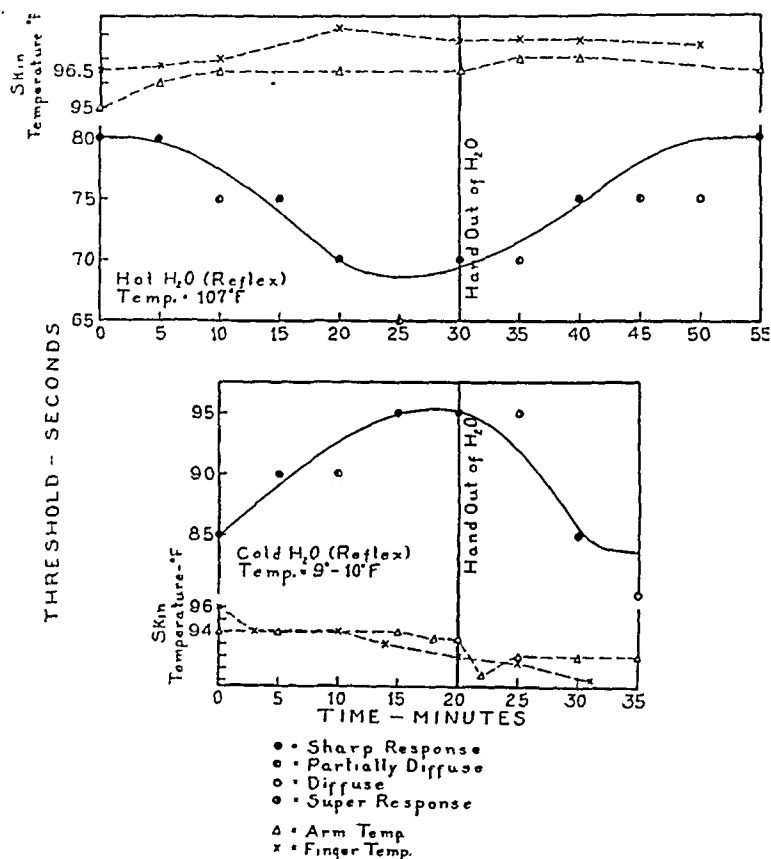


Fig. 5.—Effects on threshold reflex response to warmth (top) and cold (bottom). (See text.) (9° to 10° F. should read 9° to 10° C.)

**Reflex Effects.**—The influence of reflex response to temperature change was investigated. In these experiments, the threshold was ascertained in the usual way, at five-minute intervals, on the left arm. After the normal threshold level was established, the right hand and the arm (up to the mid-point) were immersed in water. In order to study the effect of cold the water was kept at a temperature of 9° to 12° C., and, for the effect of warmth, the temperature was 41° to 42° C. The skin temperature of the left arm and a finger of the left hand (nail bed area) was measured by means of a continuous recorder. In this way, threshold levels could be related to the reflex effects of temperature on

the circulation. Although it is now generally believed that the skin of the forearm does not participate to any significant degree in reflex readjustments to temperature changes,<sup>5</sup> it was considered desirable to record such data. The results of two experiments of this type are summarized in Fig. 5. The threshold is clearly affected by reflex responses to temperature; with cold, the threshold was raised, and, with warmth, it was lowered. The duration of the effect outlasted the period of immersion, but there was a return to normal before the skin temperatures became normal. Since slight changes in blood flow have little effect on the stimulus time (cf. above, effect of meals and exercise), one may conclude that reflex temperature adjustments have a considerable influence upon the ease with which reactive hyperemia may be induced in the skin.

These results may shed light on some aspects of the seasonal curve. Thus, the higher thresholds are found during the colder periods of the year, and the lowest thresholds, at the hottest part of the year. It appears probable that the generalized heating of the surface of the body in the summer may reflexly cause a lowering of the stimulus time threshold despite the fact that one would expect an opposite effect caused by the augmented blood flow which is known to exist under such conditions. The same reasoning holds for the winter season.

Actual analysis of the seasonal chart (Fig. 3), it should be re-emphasized, shows that the effects of warmth on the threshold curves are not immediate and do not follow the day-to-day weather fluctuations. Nevertheless, two downward steps on the threshold curves were obtained in the latter part of April and in May, and these occurred on days that were unseasonably warm. The return to cooler and more normal weather, however, marked merely a break in the downward trend of the threshold curve and not a return to the longer thresholds of a week or two earlier. These considerations pointed to the need for experimental study of a direct change in skin temperature on the threshold.

*Direct Heat.*—With a normal skin temperature of 90.2° F., the threshold for reactive hyperemia was thirty seconds, and the clearing time, forty-one seconds. After the skin was warmed by the application of external heat, and while the skin temperature was held at a level of 97.7°–98.0° F., the stimulus time was twenty-one to twenty-two seconds, and the clearing time was shortened to twenty-five seconds. Since direct heating of the arm is believed to have little effect on the rate of circulation of blood through the skin, and since we have seen that moderate changes in blood flow do not have a marked effect on the threshold, it is clear that the effect of warmth, whether applied indirectly by reflex pathways, or directly by local heating, serves to lower the threshold. The mechanisms in the two types of temperature experiments are not necessarily the same, however, and in all probability are different. Thus, in the local heating experiment, it is likely

that dilating substances are produced by the action of heat on the skin; this is believed by Lewis<sup>2</sup> to be the effect of such procedures. Because of this, a shorter period of ischemia may be expected to elicit an additive effect and so produce the rings of hyperemia. Such a mechanism cannot be imagined in the case of the reflex effects, however.

The final conclusion regarding the mechanism of reactive hyperemia as it is affected by the seasons must be elucidated by further studies. It is clear, however, that enough is now known to make certain that a seasonal variation exists, that the duration of the response may be affected by the flow of blood, and, finally, that the fluctuation in stimulus time results from a seasonal influence on the capacity of the tissues to produce a vasodilating substance, although a variation in the susceptibility of the blood vessels themselves to the same chemical stimulus has not been excluded. There is no evidence in this work to show that such a mechanism may be involved, however, and no seasonal variation has been found in the contractile sensitivity of the cutaneous blood vessels to graded mechanical stimulation.<sup>1</sup>

#### CONCLUSIONS

1. A method is described whereby the sensitivity of the smallest blood vessels of the skin to graded periods of ischemia may be measured under uniform conditions. The *stimulus time*, measured in seconds, is the minimum period of time that is required to produce three areas of uniform color, size, and sharpness. The *clearing time* is the time required for these areas of reactive hyperemia to disappear. Average values are given for individual subjects under certain conditions and seasons.

2. There was a seasonal variation in the capacity of the skin to give the reactive hyperemia response. Both the stimulation time and the clearing time lengthen progressively in the fall, and reach a high level in December which is maintained until spring. Clearing times shorten before a decrease in the stimulus time begins. The reactive hyperemia response appears to be correlated inversely with outside temperature, and possibly indoor humidity.

3. Attempts were made to ascertain the nature of various factors which might account for the seasonal variation in both stimulus and clearing times. During circulatory stasis the stimulus time is unaffected, but the areas fail to clear. During reactive hyperemia (after release from stasis) the stimulus time is lengthened, but this is shown to be the result of an increase in the rate of washing away of the dilating substance and the consequent need for more of it; this, in turn, requires a longer period of local ischemia.

4. After release from circulatory stasis, a substance is washed away from the occluded area; this lowers the threshold for the reactive hyper-

emia response in remote parts of the body, but it fails, under the conditions of these experiments, to alter blood pressure or heart rate.

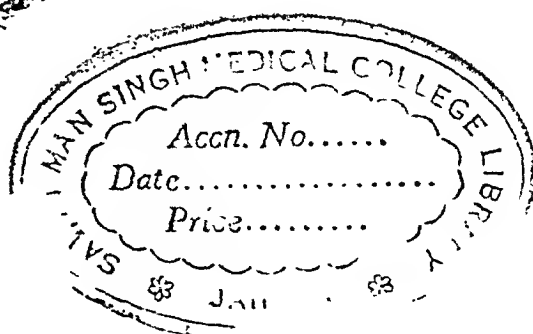
5. The role of reflex temperature effects was shown by the fact that there was an elevation of the threshold with cold, and a decrease in threshold with warmth, when the latter were applied to the opposite arm.

6. Direct heating of the skin shortens the stimulus time.

7. In the light of the above considerations, the character of the seasonal variation in reactive hyperemia responsiveness is discussed.

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# THE PATHOLOGIC PHYSIOLOGY OF THE CIRCULATION IN ACUTE THROMBOPHLEBITIS AND THE POST- THROMBOTIC SYNDROME

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THE symptoms of acute thrombophlebitis and the post-thrombotic syndrome are the logical expression of a regular sequence of alterations in the circulation of the involved extremity. The pathologic physiology which underlies these alterations involves all four of the components of the circulatory system, namely, the arterial, venous, lymphatic, and capillary (tissue fluid). The degree to which these alterations are manifest depends principally upon the location and extent of the thrombus. Comprehension of the pathologic physiology is essential in order to treat the disease properly.

## ACUTE PHASE OF THROMBOPHLEBITIS

In acute thrombophlebitis, the formation of a thrombus in a principal vein obstructs the flow of blood in this channel. Such obstruction causes damming back of the blood in the vein and its tributaries, with consequent retardation of blood flow and an increase locally in the venous pressure. Accompanying the obstruction, there is vasospasm which affects the arteries as well as the veins. The arterial spasm tends to limit the volume of blood entering the affected extremity and may further diminish the rate of blood flow in the veins. Coincident with the increase in venous pressure, there is stagnation of circulation in the lymphatics. Following these changes in the venous pressure and lymphatic flow, there are outpouring and retention of fluid in the tissue spaces. Along with the phenomena of acute venous occlusion, there is a natural tendency for the venous congestion to be relieved by routes of flow which circumvent the area of obstruction. The efficiency of the collateral circulation depends upon the location and extent of the thrombosis.

The constitutional symptoms which accompany acute thrombophlebitis vary with the virulence of the infecting organisms and the extent of the infection. Thrombophlebitis of a small segment of a superficial vein may produce no constitutional reaction. Involvement of the main venous channels of an extremity usually causes fever ranging from

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101° to 104° F. Fever may be the first evidence of thrombophlebitis, and it may rise progressively over a period of several days before local signs appear. The fever is often accompanied by chills and other manifestations of toxemia. Leucocytosis and a rapid sedimentation rate usually occur. The duration of the constitutional reaction is greatly influenced by the mode of treatment. The local reaction to acute thrombophlebitis begins with pain and tenderness, particularly along the course of the affected veins. There is rapid swelling of the extremity, with soft, pitting edema. There may be mottled cyanosis, particularly of the digits, and there may be a marked lowering of local skin temperature. The involved veins become firm and cordlike. If the superficial veins are not involved in the process, they may become more prominent and obviously distended. There may be a concomitant lymphangitis, cellulitis, and regional lymphadenitis. In cases of venous thrombosis in which there is no inflammation (phlebothrombosis), constitutional symptoms are absent, but the local circulatory changes are similar to those of acute thrombophlebitis.<sup>1</sup>

The degree of alteration of the venous circulation as a result of thrombophlebitis is primarily dependent on the location and extent of the thrombosis. Although there are numerous tributaries to each main vein, only one or two are large enough to supplant the main vein immediately. It is anatomically obvious that occlusion of a main venous channel and its principal tributary produces more severe obstructive effects than when one of the channels remains patent. For example, ligation of the femoral vein distal to the point of entrance of the saphenous does not produce sufficient obstruction to cause edema. On the other hand, ligation of the femoral vein proximal to the saphenous vein will produce edema of the affected extremity. Similarly, ligation of the axillary vein at a point distal to the site of entrance of the cephalic vein does not produce edema. In cases in which there is obstruction of a main venous channel and its principal tributary, minor tributaries acquire added importance as collateral channels. Therefore, in such cases, as thrombosis further encroaches on additional tributaries, there is an ever-increasing retardation of venous return (Fig. 1). This effect, in turn, increases the likelihood of further propagation of the thrombus.

When a vein is obstructed by thrombosis, there will be retardation of the flow of blood, with consequent congestion of the veins distal to the point of obstruction. The immediate effect of such congestion is a local rise in venous pressure. The amount of rise in venous pressure is inversely proportional to the efficiency of the collateral circulation. As the venous pressure increases, several effects occur almost simultaneously.

The involved veins become distended with blood to the point that the valves are stretched, allowing a reflux of the blood into the tributaries. By means of this reversal of blood flow, distant tributaries may



become collateral vessels in circumventing the area of obstruction. In this way a balance is again obtained between inflow and outflow of blood, but with the venous pressure persistently elevated in many cases. However, this balance is a precarious thing; a slight increase either in the amount of obstruction or of inflowing blood will disturb it, and make necessary a new readjustment at a higher level of venous pressure. The

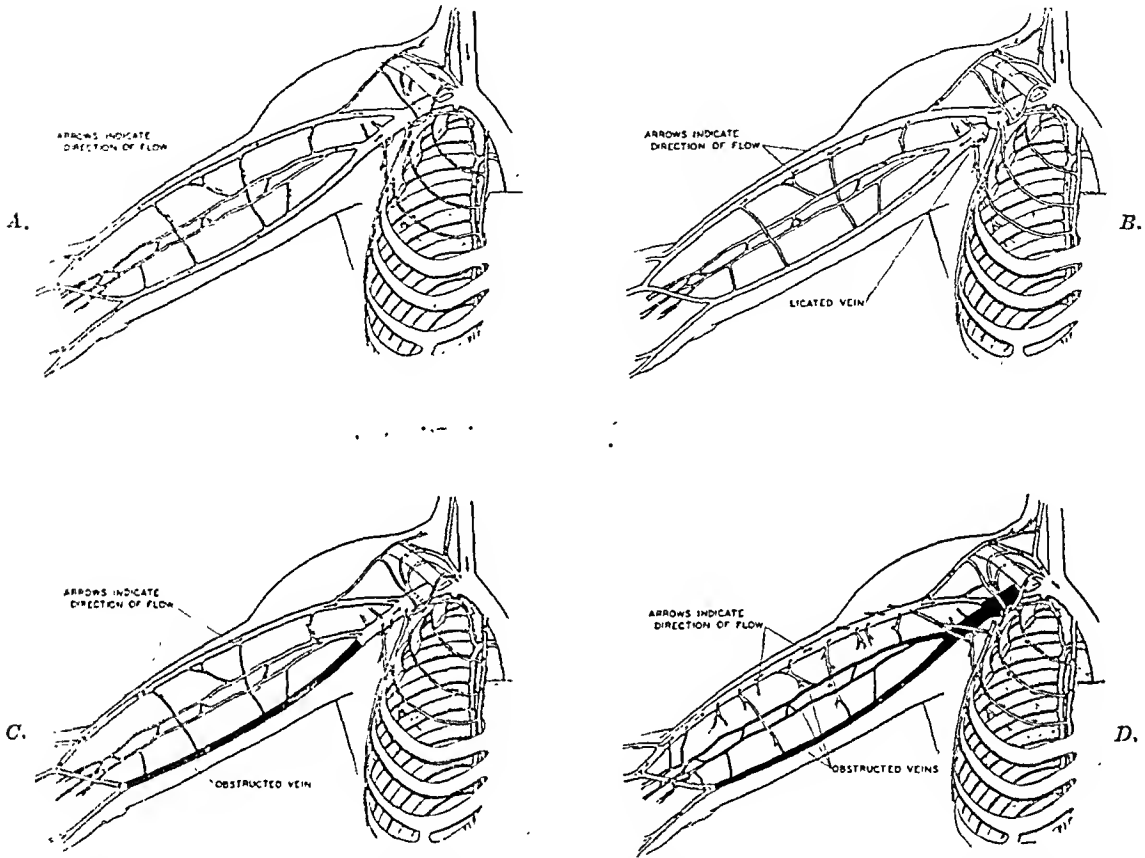


Fig. 1.—A, Schema of venous circulation of upper extremity; B, schema showing alteration in deep veins caused by ligation of axillary vein at one point; C, schema showing immediate compensation of venous return after obstruction of vein distal to points of entrance of main tributaries; D, schema showing alteration in circulation after obstruction of entire main venous trunk.

most potent factor which may upset this balance is spread of the thrombosis to such an extent that newly opened collateral channels become obstructed. The onset of menstruation is likely to precipitate spread of the thrombosis. This is apparently caused by the engorgement of the pelvic veins which occurs during this period. The position of the affected extremity is another important factor. Elevation of the extremity will tend to reduce the venous pressure, and dependency will tend to raise it, simply because of changes in hydrostatic pressure in the veins. There are other considerations, which will be discussed later, in connection with the effect of position of the extremity on the circulation. Mechanisms which increase the blood flow to the extremity have a tendency also to increase the venous pressure.

Vasospasm is probably a part of the sequence of events in every case of acute thrombophlebitis.<sup>2, 3</sup> The spasm is not confined to the damaged vessel, but involves other regional vessels, as well, probably through a reflex mechanism. The degree of spasm, however, is variable in different cases and unpredictable in any one case. Generally speaking, the more acute and widespread the thrombophlebitis, the more marked the spasm. The clinical manifestations of the vasospasm include ischemic pain and blanching and coldness of the involved extremity. The spasm may be evanescent, persistent, or recurrent.

The immediate effect of arterial spasm in thrombophlebitis is a marked reduction in the volume and velocity of blood flow in the affected extremity. This produces ischemic pain and tissue anoxemia. Undoubtedly, the most marked spasm usually occurs in the smaller arteries. However, it is not confined to these vessels. Even the main arterial trunk may be occluded by the spasm. In fact, the process may be so severe that gangrene of the extremity results. Indirectly, the slowing of the circulation caused by the spasm adds to the chances of further propagation of the thrombus and the development of emboli. The extent and exact importance of venous spasm in thrombophlebitis are difficult to appraise. In some cases, venous engorgement is obvious in the presence of severe arterial spasm. In other cases, the absence of venous engorgement may denote an accompanying venous spasm. When vasospasm lasts long enough, there may be thrombosis of the small vessels, with far-reaching effects on the ultimate results of the thrombophlebitis.

The arterial spasm may be released spontaneously or by means of certain therapeutic measures. As the acute phase of thrombophlebitis subsides, the tendency to spasm is lessened. The immediate effects of release of arterial spasm include an increase in the volume and velocity of blood flow, relief of anoxemia, and disappearance of ischemic pain. Although release of vasospasm is one of the most important factors in overcoming the immediate effects of thrombophlebitis, it must be remembered that the organic venous obstruction is not relieved. As a matter of fact, the venous pressure rises to a considerable degree (Figs. 4 and 5). This is the logical outcome of increasing the quantity of blood which enters the obstructed venous channels. However, there are certain beneficial results from augmenting the flow of blood in the veins. Increase in the rate of flow lessens the opportunity for extension of the thrombus, and the increase in the venous pressure speeds the development of collateral venous channels. The earlier the spasm is released, the better the chance for limitation of the extent of thrombosis.

The pathogenesis of edema in acute thrombophlebitis is complex. It depends upon a number of distinct factors,<sup>4</sup> all of which, however, are interdependent to some extent. In normal persons the interchange of fluid between the capillaries and tissue spaces is so well regulated

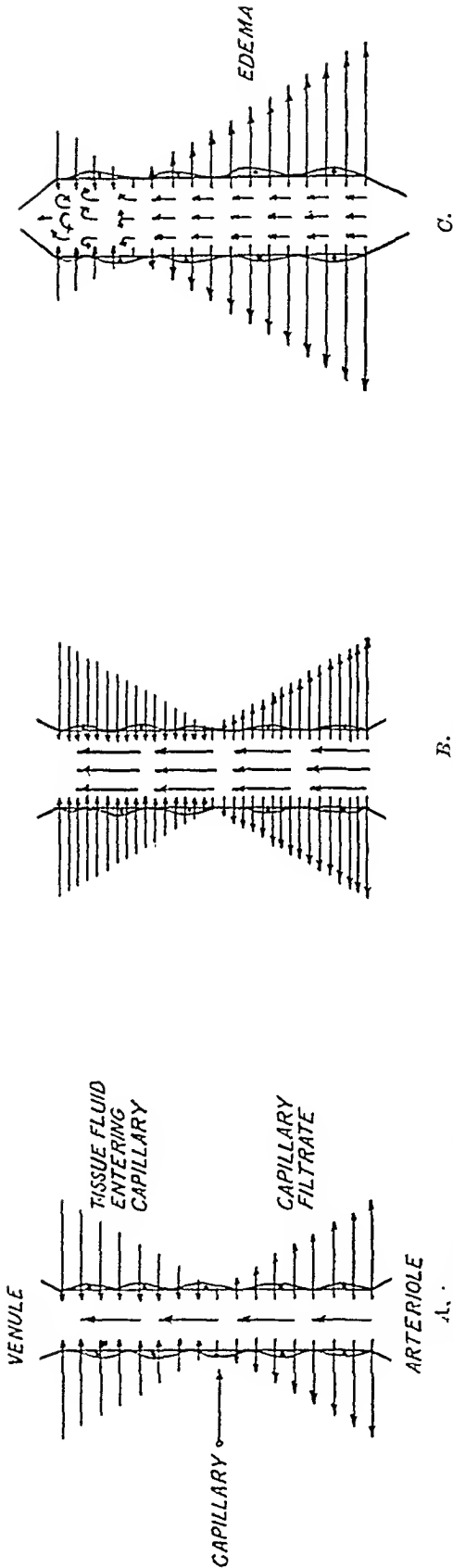


Fig. 2.—Diagram representing exchange of fluid between capillary and tissue spaces with normal circulation and in acute thrombo-phlebitis. A, Normal, resting; B, normal, exercise; C, venous obstruction while resting; D, venous obstruction with decompensation during exercise.

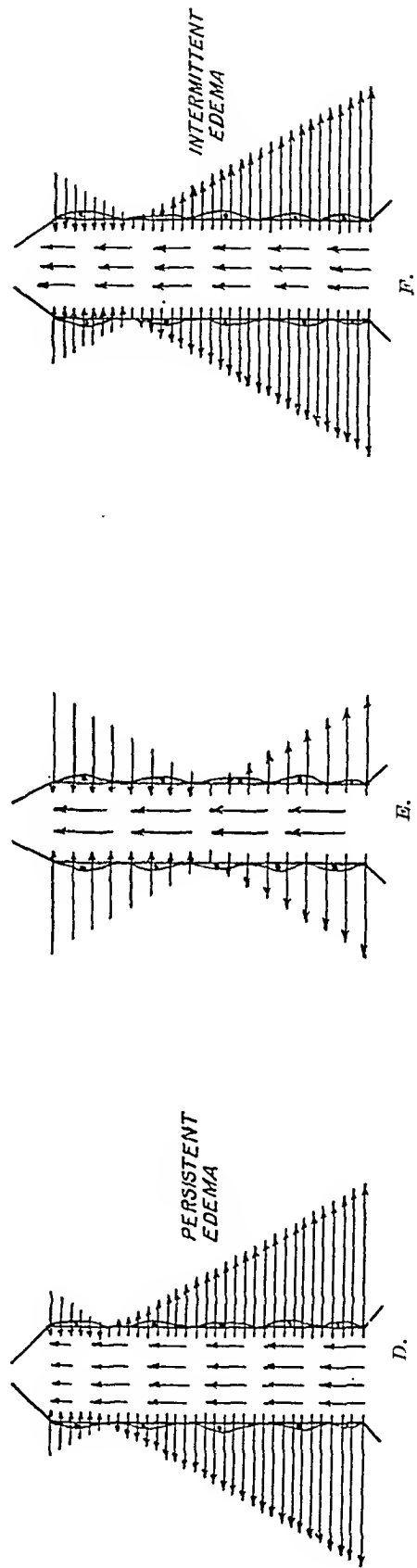


Fig. 3.—Diagram representing exchange of fluid between capillary and tissue spaces in the post-thrombotic syndrome. A, Severe persistent venous obstruction; B, normal, exercise; C, venous obstruction while resting; D, venous obstruction with decompensation during exercise.

that the volume of tissue fluid is remarkably constant. Even during exercise there is little change except an increase in the velocity of fluid exchange (Fig. 2*A* and *B*). In thrombophlebitis the prime factor in causing edema is elevation of the venous pressure;<sup>5</sup> for, when the initial readjustment of the circulation to obstruction of the veins does not result in a persistent elevation of the venous pressure, edema will not develop. On the other hand, when there is persistent and sufficient elevation of the venous pressure, increased capillary pressure results, and there is, consequently, a tendency for fluid to accumulate in the tissue spaces (Fig. 3*D*). Another important factor in the development of edema, particularly during the acute stage of thrombophlebitis, is local anoxemia of the tissues. At the onset of the venous obstruction there is an abrupt retardation of blood flow through the veins. Simultaneously, there may be arterial spasm which reduces the volume of blood flow and tends therefore to slow the current still further (Fig. 2*C*). During this stage, samples of venous blood invariably show a marked lowering of oxygen content.<sup>6</sup> As a consequence of such anoxemia, capillary permeability is increased, and there is an abnormal outpouring of fluid into the tissue spaces. There is some evidence, also, that anoxemia engenders an accumulation of tissue metabolites which increase the water-holding capacity of the tissue fluid. The degree and duration of the anoxemia depend upon the severity of the venous obstruction and the amount of arterial spasm. With the development of venous collaterals and release of arterial spasm, anoxemia tends to be relieved. A third factor in the pathogenesis of edema in acute thrombophlebitis is slowing of the lymphatic circulation. In the presence of venous obstruction and slowing of the venous flow, the lymphatic vessels become the main potential route of egress for the tissue fluid. Therefore, if flow by this route also is retarded, the tendency to edema formation is aggravated. Unfortunately, flow in the lymphatics is apparently directly dependent on an intact venous circulation, so that conditions which impede venous blood flow overburden the lymphatic circulation. Dependency of the affected part, of course, may cause the flow in the lymphatics to be further impeded. An increase in the volume of fluid in the lymphatic vessels probably causes them to become distended, so that their valves are incompetent. This process may be of such degree that the lymphatic circulation becomes completely decompensated. Apparently, the superficial lymphatic vessels are mainly affected. The ever-present tonus of the muscles continues to promote emptying of the deep lymphatics. It has been shown that the amplitude of the arterial pulse also influences lymphatic flow.<sup>7-9</sup> During the phase of arterial spasm, the effect of the arterial pulse on lymphatic flow is diminished. When vasospasm is released, one factor which contributes to lymphatic stagnation is withdrawn. It should be emphasized at this point that the lymphatic obstruction of acute thrombophlebitis is usually func-

tional and is not caused by the kind of occlusion of lymphatic vessels which may develop in the post-thrombotic syndrome. Therefore, in the earlier stage, the lymphatic obstruction is usually a reversible process; normal lymphatic circulation may be restored. In many cases, there are regional lymphangitis and lymphadenitis. These are confined to the lymphatics adjacent to the portions of the veins involved in the acute inflammatory process and to the lymph nodes draining the region. However, the regional lymphangitis and lymphadenitis probably have little effect on the lymphatic circulation in general.

It is during the acute stage of thrombophlebitis, before organization of the thrombus has begun, that embolism may occur. In some cases the thrombus may be attached firmly to the endothelium of the vein along its whole length. In other cases the thrombus is attached only in part or loosely. It is in this latter type of case that the danger of embolism is greatest.<sup>10</sup> Propagation of a thrombus from one vein into a larger vein, or from a segment of vein of a smaller caliber into another segment of larger caliber, predisposes to embolism. Such an extension of the clot is most likely to occur during the acute phase of thrombophlebitis, when blood flow is slowest as the result of vasospasm and venous obstruction.

#### POST-THROMBOTIC SYNDROME

The termination of the acute phase of thrombophlebitis may be recognized by disappearance of constitutional symptoms and local inflammatory changes. At the same time, organization of the thrombus begins. The thrombus certainly is not reabsorbed in the majority of cases. The vein tends to undergo recanalization, but this process is seldom sufficient in itself to restore normal circulation. When the acute phase has passed, the immediate results depend upon the degree to which the altered circulation has been corrected. If the thrombophlebitis has been confined to an unimportant vein or to a segment of a main vein for which adequate collateral vessels are available, there will be no permanent, significant, circulatory changes. On the other hand, if the thrombus is lodged in a main venous channel in such a location that some or all of the principal tributary veins are also obstructed, certain permanent circulatory changes will remain. These changes constitute the post-thrombotic syndrome.

The manifestations of the post-thrombotic syndrome are a logical result of the circulatory alterations. As in the acute stage, these alterations involve all four of the components of the circulation. The changes in the arterial component, however, seem to be of relatively minor importance. With subsidence of the acute phase, arterial spasm apparently disappears completely. Possibly there is even persistent dilatation of the arterioles and capillaries, although the evidence for this is incomplete. The state of the venous circulation in this stage again depends

upon the degree of obstruction and the development of collaterals. Whereas, in the acute phase of thrombophlebitis, the impairment of lymphatic circulation usually is purely functional, in the post-thrombotic syndrome an organic factor may be added. Edema is usually a prominent symptom and may be persistent or may appear only with exercise or dependency of the limb. The edema may be of the soft, pitting type or may be firm and nonpitting. Additional consequences of the persistently altered circulation in the involved extremity include recurrent thrombophlebitis, the development of varicosities, recurrent local cellulitis and lymphangitis, and a tendency to the formation of indolent ulcers.

After the obstruction of the veins, in order that the affected extremity may resume its normal function, there must be an adequate inflow of arterial blood and a prompt and adequate venous outflow. In the post-thrombotic syndrome the arterial inflow is probably adequate at all times and under varying conditions of activity. The efficiency of the venous circulation necessarily depends upon the degree and extent of venous obstruction and the competency of the collateral veins. In many cases the collateral vessels are sufficient in number, size, and distribution to compensate for the venous obstruction while the affected extremity is at rest (Fig. 3E). In these cases the venous pressure is normal, or at least below the level at which edema is produced. However, during exercise the collateral veins may be incapable of carrying away the additional blood brought in through the arteries.<sup>11</sup> The veins therefore become overfilled, and the venous pressure rises (Figs. 4 and 6). If the increment in venous pressure is great enough, there will be excessive filtration of fluid into the tissue spaces, and reabsorption of this fluid will not take place at a normal rate. If this state lasts long enough, there will be a sufficient accumulation of fluid in the tissue spaces to produce edema (Fig. 3F). When a state of inactivity is resumed, the venous circulation again serves adequately for the arterial inflow, and edema subsides. Similar changes in the venous pressure may result from placing the affected extremity in a dependent position. In women there is often an increase in the edema just before menstruation. This is frequently associated with pain in the affected extremity. We do not know whether or not this type of premenstrual edema is related to changes in the venous pressure. A similar tendency to aggravation of the symptoms of the post-thrombotic syndrome is observed during pregnancy,<sup>12</sup> and is apparently due to an increase in local venous pressure. It must be remembered that the collateral channels usually develop through superficial veins.<sup>13</sup> In such veins, the impetus imparted to the flow of blood by muscle tone is lacking, and the squeezing action of muscular exercise is ineffectual. The newly developed collaterals are usually long, tortuous, and devoid of valves. All of these factors, plus the ef-

fect of hydrostatic pressure, combine to impede the venous outflow from the dependent extremity. Since arterial inflow continues, an abnormal rise in venous pressure results. In other cases of the post-thrombotic syndrome, the collateral vessels are insufficient in size and number to compensate for the venous obstruction, even during rest in a favorable position. In such cases, because of the persistently high venous pressure, there is edema even during rest (Fig. 3D). This is aggravated by lowering the affected extremity or by exercise. Due to the congestion of the veins as the result of these factors, recurrent thrombophlebitis is more common than in normal veins.

A varicose state frequently, but not invariably, follows thrombophlebitis of the principal veins of the upper or lower extremities. When obstruction to the principal vein is in such a location and of such a degree that the pressure is increased in the superficial venous tributaries, they undergo dilatation, their valves become incompetent, and a reflux of blood flow is permitted. This process may extend to minor tributaries which are quite distant from the point of obstruction. The process is a gradual one, and varicose veins may not become clinically obvious until several months after the disappearance of the acute phase of the thrombophlebitis. The communicating veins between the superficial and deep veins also undergo dilatation, and their valves become incompetent. When this state of dilatation of the superficial veins due to high venous pressure is allowed to endure long enough, organic changes ensue in the veins and their valves.<sup>14</sup> These structural changes are irreversible, so that the varicose state of the veins persists, even though the venous pressure later becomes lowered as a result of further development of collateral circulation, or of recanalization of the vein. Another factor which influences the development of superficial varicosities is the anatomic distribution of the veins. In some normal persons the superficial veins are relatively few and relatively unimportant as channels for venous return. In such persons the opportunity for development of superficial varicosities is necessarily limited. In others the superficial veins are numerous and carry a large volume of blood. In these, large numbers of varicose veins may readily develop. Protection of the superficial venous system against dilatation may limit or prevent the development of a varicose state.

In the post-thrombotic syndrome, the importance of the lymphatic circulation in the development of symptoms is greater than in the acute phase of thrombophlebitis. In the acute phase there is a tendency to stagnation of fluid in the lymphatic vessels of the whole extremity. This is not due so much to the lymphadenitis and lymphangitis in the region of the inflamed vein. For example, acute inguinal lymphangitis and lymphadenitis often exist without producing any evidence of peripheral lymphatic obstruction. The lymphatic stagnation which accom-

panies acute thrombophlebitis is primarily due to retardation of venous blood flow and increase in venous pressure. These two factors cause an increase in the amount of tissue fluid, as mentioned above, and, consequently, the entire lymphatic system of the extremity becomes over-filled. If the venous congestion is promptly relieved, there is immediate restoration of the normal lymphatic circulation. On the other hand, if the venous pressure remains persistently elevated, structural changes similar to those in the superficial veins occur in the lymphatic vessels. Therefore, there is a kind of chronic varicose state of the lymphatic vessels, and this becomes irreversible. The walls and valves of the vessels are thickened, and there is perilymphatic fibrosis. These changes are permanent and are little affected by the development of an adequate collateral venous circulation. In other words, lymphatic stasis may persist, although the venous congestion, which originally initiated the lymphatic stasis, may have been relieved. When this state obtains, there is an increased susceptibility to infection, and frequent attacks of cellulitis and widespread lymphangitis occur. They are accompanied by fever, leucocytosis, pain, evidence of superficial inflammation in the extremity, and regional lymphadenitis. Such attacks aggravate the organic changes which are responsible for the lymphatic obstruction. With the organic lymphatic obstruction which characterizes many cases of the post-thrombotic syndrome, the skin of the affected extremity becomes thick and brawny, and does not pit on pressure. If appropriate measures are employed before the stage of organic lymphatic obstruction has been reached, a pitiful and almost hopeless state of elephantiasis usually can be prevented.

One of the more serious common consequences of the post-thrombotic syndrome is the development of ulceration in the affected extremity. Such ulcers usually occur in the region of the lower one-third of the leg, where the arterial blood supply is poorest. Occasionally they seem to occur spontaneously, but usually follow some form of local trauma, cellulitis due to acute infection, or recurrent thrombophlebitis. Once the ulcer appears, it tends to spread slowly and to become indolent. Ulceration of this type may develop whether or not varicose veins are present. The pathogenesis of the ulceration is not exactly unknown.

#### SUGGESTIONS ON THERAPY

We wish to emphasize that the prime consideration in acute thrombophlebitis is not recognition of the fact that a clot has formed in a vein, but the fact that all elements of the circulation in the affected extremity are altered as a result of the venous occlusion. The degree of this alteration will, of course, depend upon the location and extent of the thrombus and the severity of the local inflammatory process in the veins. The importance of this viewpoint in the treatment of acute



thrombophlebitis becomes apparent as soon as we realize that little or nothing can be done to influence the blood clot which has already formed. The only exception to this statement is that in certain cases it is possible to minimize the danger of embolism by ligation of the vein above the thrombus. The treatment of the disease, in general, must be directed to the relief of those changes which take place in all components of the circulation in the affected extremity.

Therapy should be primarily intended to correct the stagnation of blood and lymph flow in the involved extremity. By this means it may be possible to prevent propagation of the thrombus. There are three important measures which should be applied for the alleviation of the stagnation. They are, in the order of their importance, release of vasospasm, elevation of the extremity, and active movement of the extremity.

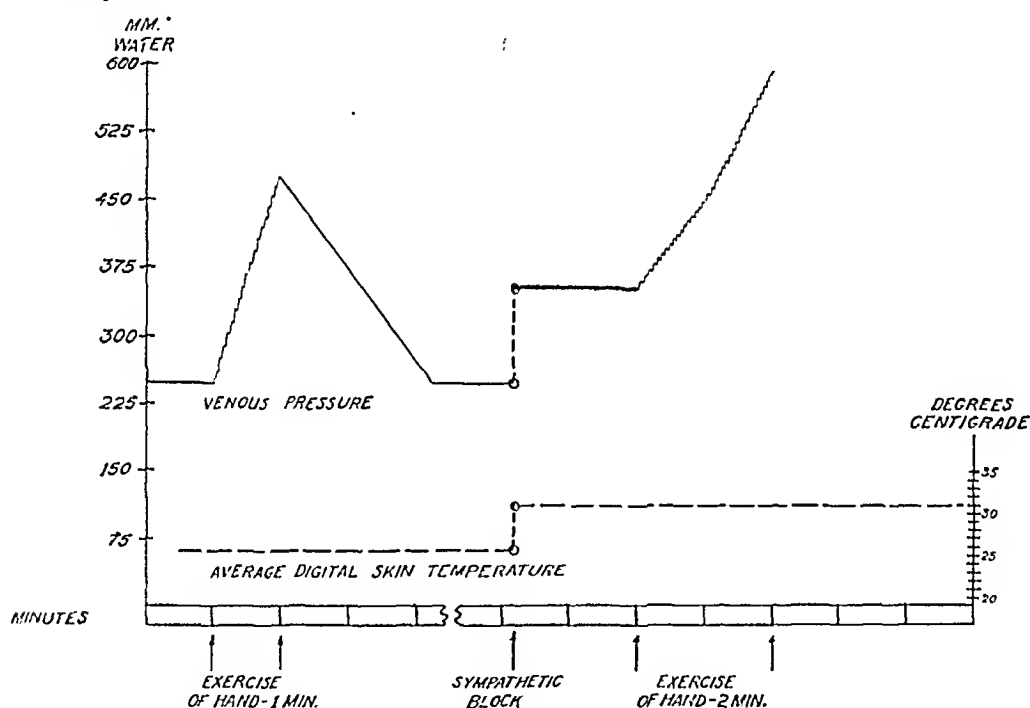


Fig. 4.—Acute thrombophlebitis of axillary and subclavian veins. Note abnormal elevation of venous pressure during rest, with prompt rise during exercise. Note the effect of sympathetic block on venous pressure and skin temperature.

Release of vasospasm and promotion of vasodilation produce a great increase in the rate and volume of blood flow in the arteries and capillaries.<sup>15</sup> The improvement in the capillary circulation tends to relieve anoxemia, and thereby removes one of the factors which influence the abnormal filtration of fluid into the tissue spaces. The increase in the amount of blood entering the veins through the dilated arteries and capillaries throws an added load on the already overfilled veins. As a result, the venous pressure actually rises, but the volume of flow through the veins is increased, mainly because of the increase in *vis a tergo* from the dilated capillary bed (Figs. 4 and 5). Possibly some improvement

results from the release of venous spasm. There is probably also an increase in lymphatic flow because of the augmentation in the amplitude of arterial pulsations which results from vasodilation. Release of vasospasm can be obtained in several ways, but not necessarily to the same degree in each. One of the measures used to overcome vasospasm is that of raising the body temperature to a febrile level. It is interesting that, in some cases of acute thrombophlebitis, local vasospasm persists

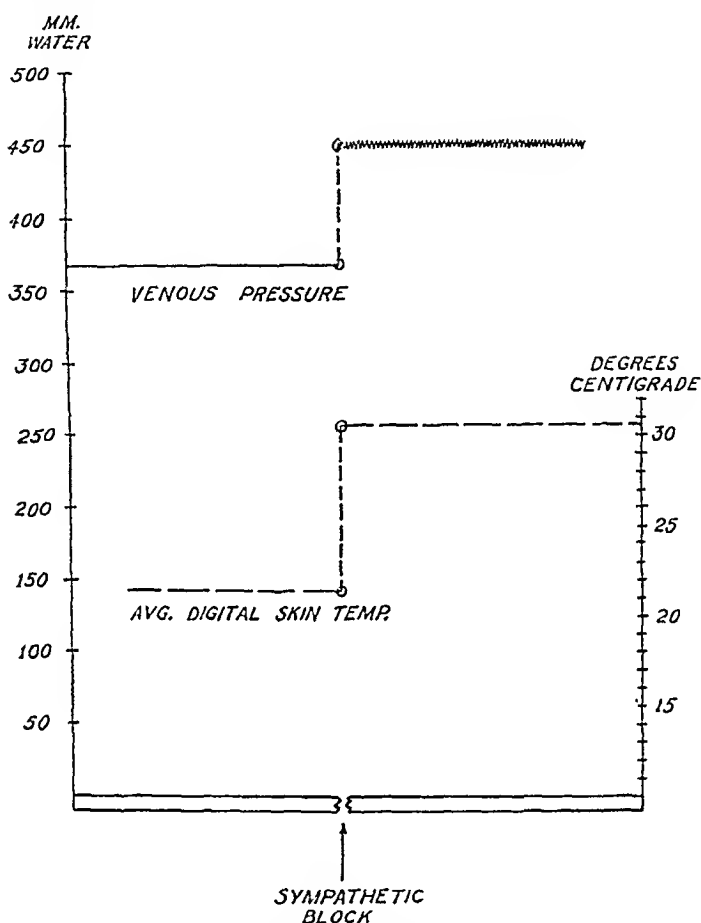


Fig. 5.—Acute iliofemoral thrombophlebitis. Note high initial venous pressure and low skin temperature. Sympathetic block produced increase in venous pressure and rise in skin temperature.

in spite of a rise in body temperature to  $103^{\circ}$  or  $104^{\circ}$ . In such cases, a further increase of body temperature by artificial means does not seem warranted. Some other measure which acts directly on the local spasm must be instituted. It is to be emphasized that complete release must be secured. If one measure does not suffice, additional procedures must be employed (Fig. 7). It must also be emphasized that the release of vasospasm, a return of the patient's temperature to normal, and the disappearance of edema while the patient is at rest in bed cannot be accepted as summary evidence that the derangement of the circulation has been completely corrected.

Elevation of the affected extremity above the level of the heart tends to remove the factor of hydrostatic pressure. Emptying of the veins and lymphatics is thereby enhanced.

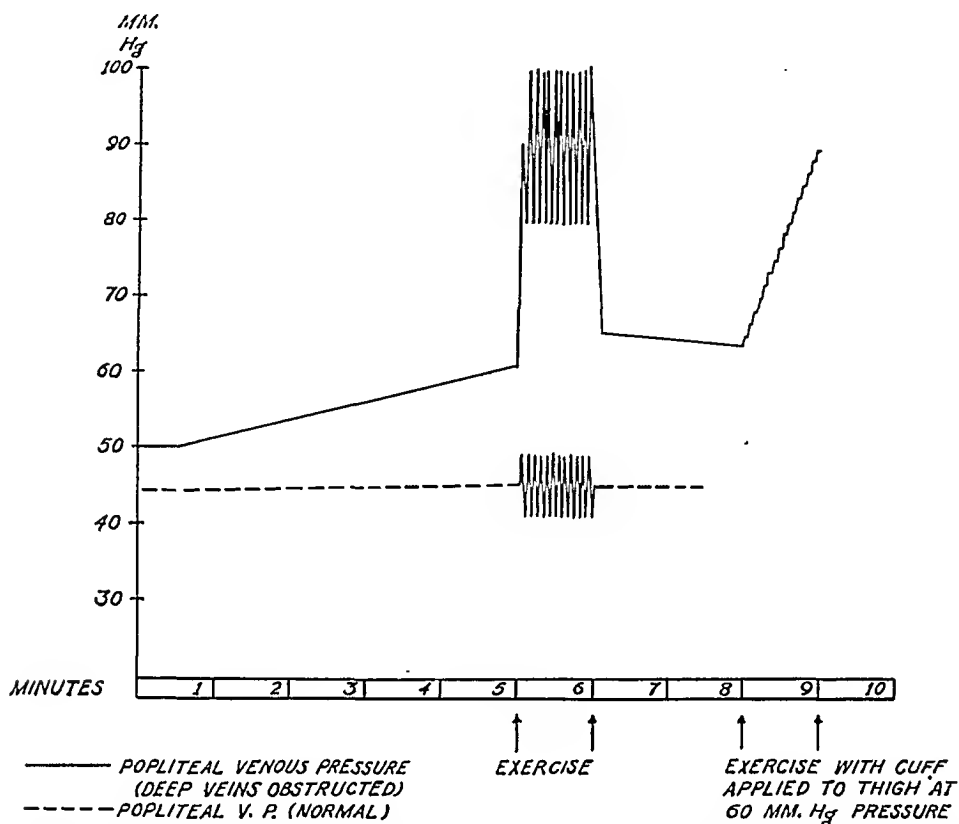


Fig. 6.—Post-thrombotic stage of iliofemoral thrombophlebitis. Note the extreme elevation in venous pressure on the affected side during exercise as compared to the normal fluctuation on the unaffected side. The extreme oscillations in venous pressure on the obstructed side during exercise were apparently due to incompetency of the communicating veins, as demonstrated by disappearance of the wide excursions when the superficial veins were occluded by means of a tourniquet.

Active motion of the extremity by the patient promotes emptying of the lymphatics and veins. Furthermore, it improves the circulation by increasing the rate and volume of arterial blood flow. The danger of embolism as a result of dislodgment of a portion of a thrombus caused by movement of the affected extremity is often postulated. In our own experience, the opposite has been true. Prolonged immobility seems to favor extension of the thrombus beyond its fixed point in the area of phlebitis, and, since the extended portion is not fixed to the vein wall, it may be dislodged.

Pain in thrombophlebitis is of two types. There is pain at the site of the thrombosed veins which is due to the local inflammatory reaction. There is also general pain in the affected extremity which is probably due to anoxemia caused by vasospasm. The latter type of pain is promptly banished when the anoxemia is relieved by measures which produce vasodilation.

The relief of edema is accomplished in part by the same measures which tend to overcome stagnation of blood and lymph flow, namely, release of vasospasm, with consequent elimination of anoxemia, and elevation and active movement of the extremity. Nature soon comes to the aid of the physician by developing collateral venous channels.

When the proper measures, as mentioned above, are instituted, the local thrombophlebitis is limited, and usually the constitutional symptoms rapidly subside. Occasionally the inflammatory process becomes suppurative, in which case the systemic symptoms of inflammation are correspondingly protracted.

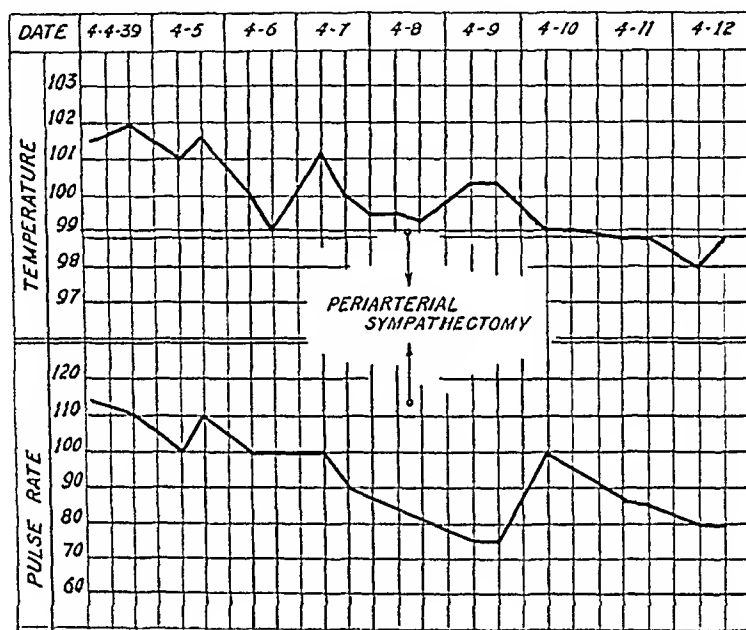


Fig. 7.—Post-partum iliofemoral thrombophlebitis. Acute pain in region of lower part of thigh and knee, cyanosis of entire extremity, and absence of femoral pulsation simulating arterial embolism. Exploration of femoral vessels revealed thrombophlebitis, with spasm of artery. Periarterial sympathectomy immediately restored pulsations and relieved ischemic pain.

It is almost unnecessary to point out the importance of early treatment of acute thrombophlebitis. When stagnation of venous flow is prolonged, the opportunity for propagation of the thrombus is increased, and the circulatory changes are consequently more severe. In turn, the possibilities for restoration of a normal circulation are more limited.

Once the post-thrombotic stage of acute thrombophlebitis has been reached, the attitude of patient and physician toward treatment of the affected extremity too often becomes apathetic. Many times the physician expresses his attitude toward the disease by complete inactivity. He assumes that the patient is doomed to all of the undesirable complications which we have described above. Frequently the process is relegated to the status of those conditions which can be observed while "nature takes its course." Although the importance of natural

processes of repair cannot be underestimated, it is nevertheless true that a great deal of assistance to recovery can be given, and that, by proper treatment, based on a knowledge of the character of the circulatory changes, many of the undesirable complications can be minimized or wholly prevented.

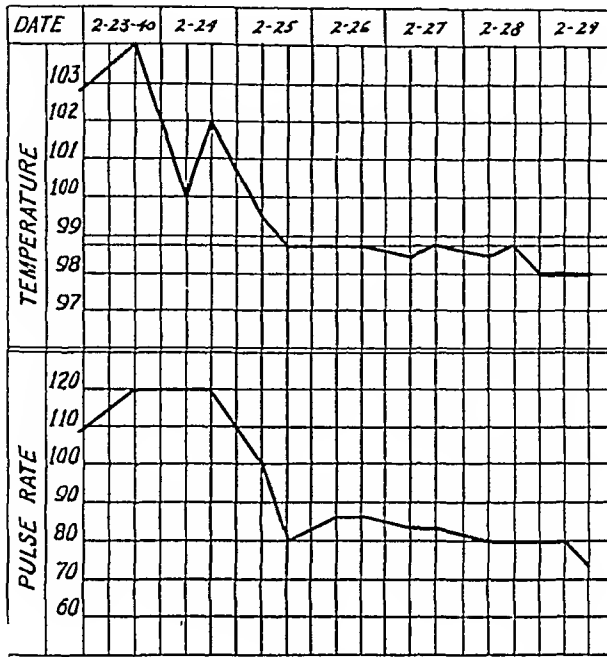


Fig. 8.—Post-thrombotic syndrome, with recurrent cellulitis. Lymphangitis, and lymphadenitis. Severe constitutional and local reaction. Treatment by rest in bed, warm compresses, and sulfanilamide.

Treatment of the post-thrombotic syndrome should begin before the patient with acute thrombophlebitis is allowed to resume his normal activities. The most important therapeutic measures are those which encourage the development of a collateral channel and tend to prevent overfilling of the superficial veins and lymphatics. These measures should include the use of pressure bandages of some type. The bandage should be applied with a pressure which is sufficient only to compress the superficial veins and lymphatics. A bandage which impedes arterial circulation even slightly is to be condemned. On the other hand, any type of bandage which does not produce a uniform compression of the superficial vessels is useless and may be harmful. In our experience the most efficient type of bandage is a properly fitted elastic stocking. By this means, the superficial veins and lymphatics are prevented from becoming abnormally dilated, and edema is limited. Prevention of dilatation of the superficial veins encourages the development of deep collateral vessels. This is desirable because the deep veins carry blood more efficiently during muscular activity and do not tend to become varicose. The same is true with respect to the lymphatics.

Recurrent thrombophlebitis, cellulitis, and lymphangitis are common in an extremity in which the superficial vessels are allowed to become dilated. These complications, as well as edema, predispose to the development of ulceration. Therefore, if the superficial vessels are prevented from becoming dilated, there is less likelihood of recurrent thrombophlebitis, cellulitis, lymphangitis, and ulceration. Treatment of the attack of cellulitis and lymphangitis by rest in bed, elevation of the extremity, the local application of moist, warm compresses, and the administration of sulfanilamide often gives spectacular results (Figs. 8 and 9).

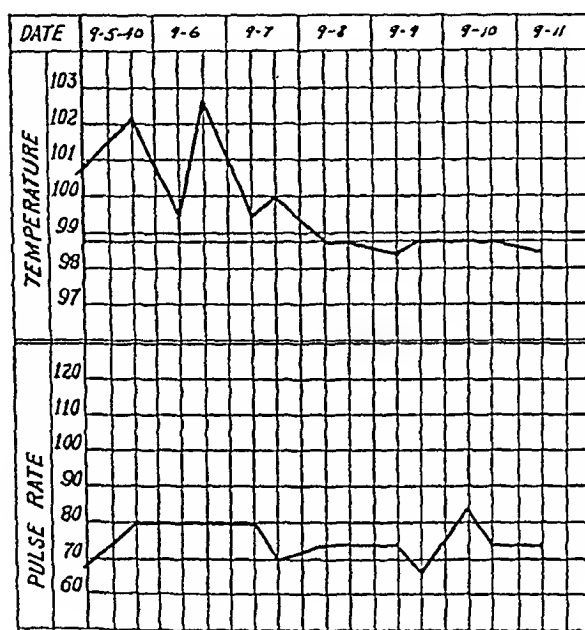


Fig. 9.—Post-thrombotic syndrome, with recurrent cellulitis and lymphangitis. Mild constitutional and local reaction. Treatment by rest in bed, warm compresses, and sulfanilamide.

Active surgical measures which involve any part of the venous circulation have no place in the therapy of the post-thrombotic syndrome as long as the venous pressure in the affected extremity is abnormally high at rest, or becomes abnormally high during exercise (Fig. 6). As a matter of fact, surgical interference with the veins under these conditions is a form of undesirable meddling.

The patient must be made to understand the objects of therapy in the post-thrombotic syndrome. He must realize that the length of time required for the accomplishment of these objects is necessarily variable and unpredictable, but that in any case it will be prolonged over a period of months, or even years. The physician must realize that treatment must be continued as long as there is any evidence of derangement of the circulation in the arteries, veins, lymphatics, and tissue spaces.

## CONCLUSIONS

In acute thrombophlebitis and the post-thrombotic syndrome all components of the circulatory system in the affected extremity are implicated in the production of symptoms. The degree to which each component is affected varies with the stage of the disease. In a larger sense, the effects of the circulatory involvement depend fundamentally upon the location and extent of the thrombotic process. Treatment of the effects of thrombophlebitis and the post-thrombotic syndrome can be logical only when the nature of the alterations in the physiology of the various components of the circulation is thoroughly understood.

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## DISCUSSION

DR. A. W. DURYEE, New York, N. Y.—I should like to compliment Dr. Veal and Dr. Hussey on their excellent presentation. I should also like to suggest that there are perhaps two other factors that influence the development of thrombophlebitis, especially in the upper extremities, which must be considered in the treatment of the post-thrombophlebitic state.

One of these factors is the variation in development of the venous system. Those who have done many venograms realize that the arrangement of the veins in the arms and legs varies tremendously.

Another factor of importance in the upper extremities is that muscle abnormalities and bone abnormalities in the region of the shoulder may obstruct venous return. One may find, in an apparently normal person, an elevated venous pressure which can be explained only by muscle or bone pressure on the veins. If any surgical operation is performed on these patients, especially in the post-thrombophlebitic stage, the procedure which is indicated is release of the pressure by scalenectomy or some similar operation.

DR. GEZA DE TAKATS, Chicago.—In addition to the therapeutic measures which Dr. Hussey has discussed, I should like to mention briefly two very simple methods which have proved to be of great help to us in the management of acute thrombophlebitic edema. One is the use of diuretics. As you know, if edema is allowed to persist, a state of thrombophlebitic induration may develop.

The other measure which we have used to great advantage in the treatment of periphlebitis and lymphangitis is small doses of roentgen therapy over the affected area, usually in the iliofemoral regions, but sometimes over the calf muscles.

There is one more point I should like to emphasize in connection with the late sequelae of thrombophlebitic edema, and that is that the interference with the circulation is due not only to the fact that persistent, chronic vasospasm may be present, or that veins may be occluded, or that lymphatic destruction exists, but to the fact that such a potent reflux of blood occurs in the standing position that it is almost impossible to treat.

Before this Society I had the pleasure of discussing a paper by Dr. Edwards, who showed that every time larger veins are occluded the valves are destroyed, and, even if canalization occurs, the valves become insufficient. We have seen patients with beginning of thrombosis who came back later showing not as much deep venous obstruction as deep venous insufficiency; that is to say, a great amount of blood would fill up the lower extremity because the valves in the iliac or femoral veins were incompetent. We have been unable up to the present time to find any solution of the therapeutic problem, except by bandaging.

DR. NORMAN E. FREEMAN, Philadelphia.—I believe Dr. Veal and Dr. Hussey have done a splendid piece of work in bringing together these facts on venous obstruction. There are two aspects of this question which I should like to take up very briefly.

The first is the question: Is there arterial spasm in the acute stages of thrombophlebitis? I believe that, in a small number of cases, there is actually enough arterial spasm to produce arterial insufficiency. However, in my experience, the general picture of acute thrombophlebitis, especially the mild type, not the massive iliofemoral thrombosis, shows an increase of blood flow to the part. There is a rise in skin temperature. There is an increase in oscillations, and, as Dr. De Takats has pointed out, the sole of the foot on the involved side is warmer than that on the normal side.

Linton, last year, at the Vascular Section meetings, presented an interesting experimental demonstration of the fact that obstruction of the venous return would actually increase the arterial flow into the affected part. There are controversies as to the mechanism of this increase in blood flow which is associated with venous occlusion, but his experimental demonstration fits in with our clinical observation that there are a rise in skin temperature and an increase in the oscillations on the affected side.



As far as treatment is concerned, we realize that simple ligation of a vein, even the femoral vein, is accompanied by less deleterious and less disastrous results than thrombophlebitis. In one of my cases, this thrombophlebitis finally went on to gangrene. At the time the leg was amputated it was found that there was extensive arborization thrombosis of the venous radicals, extending all the way down the femoral to the popliteal vein. In the branches of these veins there was extension of the thrombotic process.

The amount of disability that patients will suffer in the postphlebotic stage does depend to a certain extent upon the amount of thrombosis which takes place, and so I feel that the efforts that Dr. Veal has mentioned, which are designed to limit the thrombosis, are of great significance.

One additional procedure in the treatment of acute thrombophlebitis may be worth while, namely, tight compression of the involved extremities with elastic bandages while the patients are in bed immediately after the acute thrombophlebitis has taken place. It may be that in this way we can prevent the arborization thrombosis.

There was a question in our minds as to whether it was advisable to limit the return circulation still further by applying pressure to the superficial veins, but the fact that there was evidence of increased circulation, as shown by skin temperature and by the oscillogram, suggested that there were collateral channels available when the main return channel was blocked, for the increase in temperature must mean that there was more blood coming out of the leg, as well as more blood going into it. We knew that, under such circumstances, the venous pressure would rise until it met diastolic pressure, and therefore we did not apply enough pressure to occlude the arterial flow, for we realized that there was available venous collateral circulation to take the blood back.

In closing, I should like to say a word about the use of heparin, which has not been mentioned today. Dr. Gordon Murray, in Toronto, has employed it routinely in his cases of severe iliofemoral thrombophlebitis. We have had experience with it in about twenty-five cases, and we feel that it does help to put a stop to the arborization thrombotic process, and so may help to cut short the severe disability which these patients experience in after months.

DR. EDGAR A. HINES, Rochester, Minn.—It is my impression that the sulfonamides have not been of very great value in the treatment of acute thrombophlebitis, particularly in postoperative thrombophlebitis. I have observed a number of cases in which thrombophlebitis has developed during adequate sulfonamide therapy.

Would Dr. Hussey comment regarding this type of therapy? I noted from his slides that he had given some of his patients sulfanilamide.

DR. J. ROSS VEAL.—With respect to the remarks of Dr. de Takats, we have had no experience with roentgen therapy and diuretics in cases of acute edema in thrombophlebitis.

Dr. Freeman mentioned elastic bandages. That brings up one of the most important points in the treatment of thrombophlebitis. So many types of bandages are on the market that I am afraid most of them are used improperly. Many patients who come into the hospital wearing very tightly applied, so-called "Ace" bandages, or other kinds of bandages which contain a compound that sticks to the skin, have ulcerations under the bandages. We feel that bandages should be just sufficiently tight (uniformly over the whole extremity) to compress the veins and

superficial lymphatics, without interfering with the arterial blood supply. Tight bandages do serious harm, and loose bandages have no beneficial effect whatsoever.

Dr. Freeman mentioned skin temperatures in acute thrombophlebitis. The striking thing about this is that the patients differ greatly; one will have a cold extremity, and another may have a warm extremity. Why this is so we do not know, but, in our experience, there is usually some evidence of vasospasm during the acute phase of thrombophlebitis, and we believe that this depends upon the degree or extent of thrombosis of the large veins.

Dr. Hines mentioned sulfanilamide. We have found that this drug does little good in the acute stages of thrombophlebitis, but it works very well in the acute post-thrombotic stages.

# BLOOD PRESSURE STUDIES ON NEGRO AND WHITE MEN AND WOMEN LIVING IN THE VIRGIN ISLANDS OF THE UNITED STATES

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DURING 1939 and 1940, clinical examinations, including blood pressure observations, of a large proportion of the population of the Virgin Islands were made. It is the purpose of this article to analyze the blood pressure observations and to compare them with studies made in the United States and elsewhere.

## DESCRIPTION OF AREA

The Virgin Islands of the United States are situated in the Caribbean Sea, about 40 miles east of Puerto Rico. There are three main islands in the group, namely, St. Thomas and St. John, which lie together between Puerto Rico and the British Virgin Islands, and St. Croix, which is about 40 miles south of St. Thomas. The climate, which may be described as subtropical, is agreeable and pleasant, with temperatures ranging from 68° F. to 92° F., and a mean annual temperature of about 80° F. The average rainfall amounts to approximately 46 inches a year, but frequent and severe droughts occur. The inhabitants number nearly 25,000, of whom only 700 live on St. John; the remainder are about equally divided between St. Thomas and St. Croix. About 70 per cent are negroes; 20 per cent are colored, and the remaining 10 per cent are white or Puerto Ricans, most of whom are of mixed Indian, white, and negro blood. General health conditions in the Virgin Islands compare very favorably with the other West Indies islands, and tropical diseases are rare except for occasional cases of malaria and dysentery, and filariasis, which is prevalent in St. Croix.<sup>1</sup> Yaws does not occur, but syphilis is present in about 16 per cent of the entire population, i.e., in 18 per cent of the negroes, and 4 per cent of the whites.<sup>2</sup> Because the islands are very poor, and do not yield agricultural products in any quantity, the general diet is inadequate in kind, although the amount seems sufficient to keep the majority of the people well nourished. As a result, the general health suffers, and deficiency diseases are relatively common, especially pellagra and skin and eye changes due to lack of vitamin A.

<sup>1</sup>The observations upon which this study is based were conducted under the auspices and with the support of the Leonard Wood Memorial and were aided by a W.P.A. project.

<sup>2</sup>Received for publication Aug. 2, 1941.

## METHODS OF STUDY

In St. Thomas, during 1939, the entire population of nearly 11,000 was included in a house-to-house census, and about 7,200 were examined in the clinic. In St. Croix, during 1940, a census was taken of a rural population group, numbering about 5,100, of whom nearly 4,800 were examined. In St. Thomas, blood pressure observations were made routinely on all examined persons who had reached the age of 15 years; whereas, in St. Croix, blood pressure readings were made only as time permitted, and without selection as to age or physical condition. The combined group from the two islands on whom readings were made probably represents a good random sample of the entire population. All readings were made with a standard mercury sphygmomanometer, with the patient either sitting in a chair with the arm resting on a table about breast-high, or in a reclining position. Readings were made several minutes after the patient had entered the examining room and a brief medical history had been taken. The level of the appearance of the first sound was recorded as the systolic pressure, and the change in sound as the diastolic pressure. Readings were frequently repeated if they appeared to be unusual.

Because the colored group was small and showed little difference in blood pressure, they are included with the negroes. The white population is considered separately because their blood pressure readings were consistently different from those of the negroes. The small group of Puerto Ricans is not included. Blood pressure observations were recorded on 4,913 persons (4,374 negroes and 539 whites), representing more than 50 per cent of the enumerated population over 15 years old.

## OBSERVATIONS

*Systolic Blood Pressure.*—The mean systolic pressure of negroes and whites, by sex and age, is recorded in Tables I and II, and the systolic pressure of negroes is shown in Fig. 1. The level for male negroes rose steadily, with age, from 120 mm. between the ages of 15 and 19 years to 164 mm. among those who were 65 to 69 years old, after which there was a decrease. For females the level was essentially the same as that of males up to the age of 35 years, after which it began to increase more rapidly than in males; it reached a peak of 184 mm. between the ages of 70 and 75 years, and then decreased. The standard deviation increased in both sexes from a level of about 14 mm. among the younger persons to more than 30 mm. in old age, which is indicative of the greater range of readings with advancing age. The mean for all ages for males was  $138.62 \pm 0.68$ ; and for females it was  $147.05 \pm 0.68$ . After standardization for age, the mean for males became 138.92, and, for females, 146.10, which is a difference of  $7.18 \pm 0.96$ . This indicates that, among negroes, females have a significantly higher mean systolic blood pressure than males.

Among white persons, the systolic blood pressure likewise increased with age. The mean, standardized for age, was 126.51 mm. for males, and 133.30 mm. for females, which is a difference of 6.79 mm.  $\pm 1.99$ . Here, again, the general average was significantly higher in females than in males. A comparison of mean systolic pressure, standardized for age, reveals that the pressure for both sexes among negroes was

considerably higher than among whites; male negroes had a mean systolic pressure 12.41 mm. higher than male whites; and female negroes had a mean systolic pressure 12.80 mm. higher than female whites.

TABLE I  
MEAN SYSTOLIC BLOOD PRESSURE OF NEGROES, BY SEX AND AGE

| AGE<br>(YEARS)                         | MALES |                   |                                    | FEMALES |                   |                                    |
|--|-------|-------------------|------------------------------------|---------|-------------------|------------------------------------|
|  | NO.   | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE | NO.     | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE |
| 15-19                                  | 240   | 120.39            | 17.21                              | 315     | 123.14            | 14.28                              |
| 20-24                                  | 268   | 123.48            | 14.74                              | 287     | 123.27            | 14.41                              |
| 25-29                                  | 222   | 128.72            | 19.93                              | 274     | 126.41            | 16.10                              |
| 30-34                                  | 155   | 131.47            | 20.00                              | 214     | 131.22            | 20.06                              |
| 35-39                                  | 146   | 132.29            | 22.56                              | 216     | 141.21            | 26.85                              |
| 40-44                                  | 122   | 143.44            | 27.07                              | 216     | 146.66            | 28.75                              |
| 45-49                                  | 139   | 149.77            | 31.89                              | 209     | 159.34            | 33.73                              |
| 50-54                                  | 133   | 149.76            | 32.32                              | 220     | 168.50            | 42.67                              |
| 55-59                                  | 135   | 158.94            | 35.57                              | 199     | 173.83            | 33.61                              |
| 60-64                                  | 126   | 160.63            | 33.25                              | 143     | 177.88            | 32.25                              |
| 65-69                                  | 81    | 164.04            | 29.90                              | 102     | 182.50            | 31.79                              |
| 70-74                                  | 39    | 160.83            | 31.08                              | 67      | 183.91            | 36.69                              |
| 75-79                                  | 26    | 146.35            | 36.25                              | 40      | 177.12            | 35.43                              |
| Over 80                                | 17    | 163.09            | 30.71                              | 23      | 166.19            | 24.20                              |
| Total                                  | 1,849 | 138.62            | 29.34                              | 2,525   | 147.05            | 34.14                              |
| Mean<br>(stand-<br>ardized<br>for age) |       | 138.92            |                                    |         | 146.10            |                                    |

TABLE II  
MEAN SYSTOLIC BLOOD PRESSURE OF WHITE PERSONS, BY SEX AND AGE

| AGE<br>(YEARS)                         | MALES |                   |                                    | FEMALES |                   |                                    |
|--|-------|-------------------|------------------------------------|---------|-------------------|------------------------------------|
|  | NO.   | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE | NO.     | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE |
| 15-19                                  | 39    | 117.65            | 12.20                              | 22      | 123.87            | 10.89                              |
| 20-24                                  | 39    | 118.15            | 11.50                              | 30      | 120.17            | 9.10                               |
| 25-29                                  | 33    | 124.15            | 13.10                              | 28      | 124.83            | 14.30                              |
| 30-34                                  | 36    | 124.15            | 15.55                              | 33      | 124.32            | 11.54                              |
| 35-39                                  | 37    | 133.20            | 18.50                              | 23      | 126.64            | 14.64                              |
| 40-44                                  | 29    | 131.30            | 17.85                              | 25      | 125.70            | 13.41                              |
| 45-49                                  | 20    | 138.75            | 25.20                              | 30      | 137.00            | 19.25                              |
| 50-54                                  | 25    | 143.50            | 28.92                              | 17      | 141.33            | 25.70                              |
| 55-59                                  | 17    | 151.90            | 32.67                              | 14      | 155.00            | 22.66                              |
| 60-64                                  | 7     | 163.95            | 27.83                              | 19      | 165.65            | 35.59                              |
| 65-69                                  | 8     | 149.40            | 29.12                              |         |                   |                                    |
| Over 70                                |       |                   |                                    | 8       | 163.75            | 25.58                              |
| Total                                  | 290   | 130.30            | 22.80                              | 249     | 133.03            | 23.11                              |
| Mean<br>(stand-<br>ardized<br>for age) |       | 126.51            |                                    |         | 133.30            |                                    |

Although the mean systolic pressure is valuable, it may be unduly weighted by a few very high or very low readings. Also important is the percentage of persons with blood pressures above one level and below another. We have arbitrarily used 150 mm. and 110 mm. for the upper

and lower levels because we were able to find comparative studies in which these figures had been chosen. Table III and Figs. 2 and 3 show the percentage of negroes of both sexes with a systolic blood pressure of 150 mm. or more, or less than 110 mm. The proportion with high blood pressures increases very markedly, with age, from a low to a very high level, with a male preponderance after 50. When only pressures below 110 mm. are considered, the reverse is true, namely, the proportion

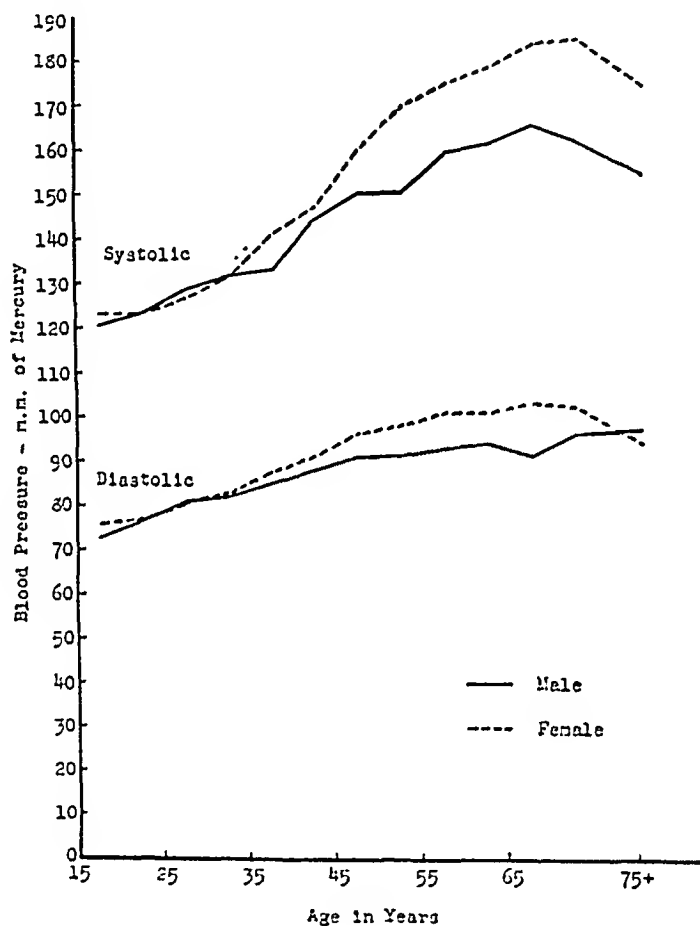


Fig. 1.—Mean systolic and diastolic blood pressure by age in Virgin Islands negroes.

with low blood pressure is large in early life and decreases to a low level in later life, with an excess of "low-pressure" males at all ages. This probably indicates that the mean systolic values which we obtained were not unduly influenced by very high or very low pressures. Considerably more than 50 per cent of all persons between the ages of 15 and 50 years have a systolic blood pressure between 110 mm. and 150 mm., but after the age of 50 years the most common level is above 150 mm.

A special analysis was made of blood pressure in negroes in relation to age and weight. Table IV shows mean systolic blood pressure for

TABLE III

PERCENTAGE OF NEGROES WITH SYSTOLIC BLOOD PRESSURE ABOVE 150 MM., AND BELOW 110 MM., BY SEX AND AGE

| AGE<br>(YEARS) | PERCENTAGE ABOVE<br>150 MM. |         | PERCENTAGE BELOW<br>110 MM. |         | PERCENTAGE<br>110-150 MM. |         |
|----------------|-----------------------------|---------|-----------------------------|---------|---------------------------|---------|
|                | MALES                       | FEMALES | MALES                       | FEMALES | MALES                     | FEMALES |
| 15-19          | 5.0                         | 2.2     | 24.2                        | 17.8    | 70.8                      | 80.0    |
| 20-29          | 8.4                         | 4.5     | 18.6                        | 16.4    | 83.0                      | 79.1    |
| 30-39          | 18.6                        | 17.2    | 14.6                        | 8.8     | 66.8                      | 74.0    |
| 40-49          | 41.0                        | 39.1    | 9.2                         | 2.4     | 49.8                      | 58.5    |
| 50-59          | 49.6                        | 62.3    | 4.9                         | 1.0     | 45.5                      | 36.7    |
| 60-69          | 59.4                        | 73.5    | 2.9                         | 0.4     | 37.7                      | 26.1    |
| Over 70        | 66.7                        | 73.1    | 4.2                         | 0.0     | 29.1                      | 27.0    |

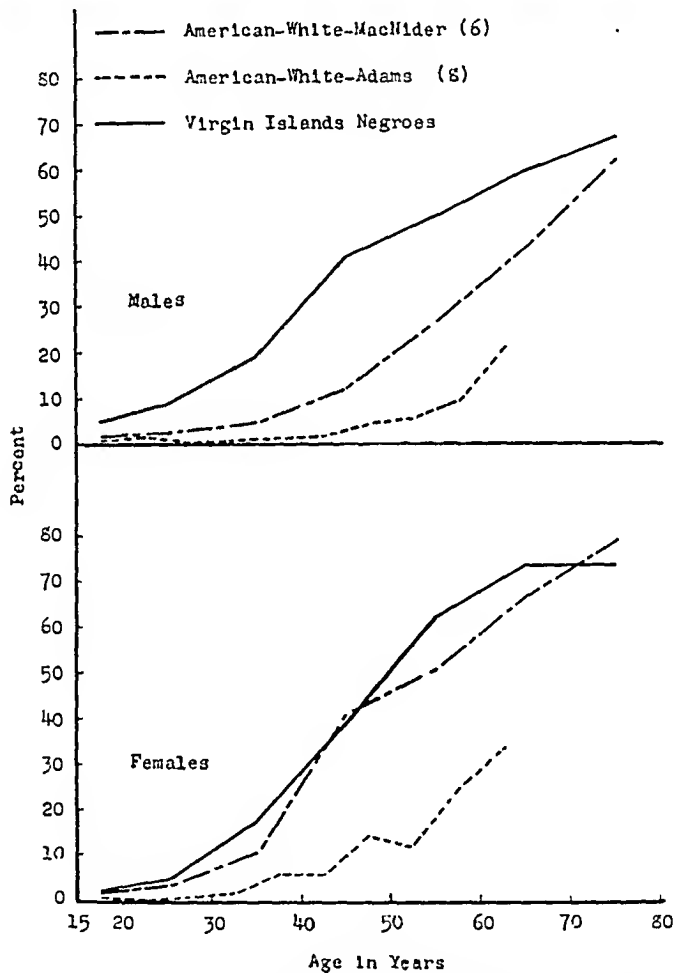


Fig. 2.—Percentage of males and females by age having systolic blood pressure of 150 or more mm. of mercury.

males and females of different weights in many age groups. There was a slight increase in each age group with increasing weight, but the increase in pressure was much more marked with increasing age. Correlations were made for each sex between systolic blood pressure, age, and weight. The correlation coefficient of mean systolic blood pressure with weight, for persons 15 to 69 years old, was  $0.1360 \pm 0.0241$  for

males, and  $0.2327 \pm 0.0200$  for females, which indicates a very low degree of correlation between systolic pressure and weight for both males and females. The correlation coefficient of mean systolic blood pressure with age, for the same age group, was  $0.5039 \pm 0.0177$  for males and  $0.7367 \pm 0.00934$  for females, which represents a fairly high correlation in both sexes. The correlation coefficient for weight with age was  $0.0517 \pm 0.0245$  for males, and  $0.2098 \pm 0.0202$  for females, which indicates no correlation between age and weight in males, but a slight

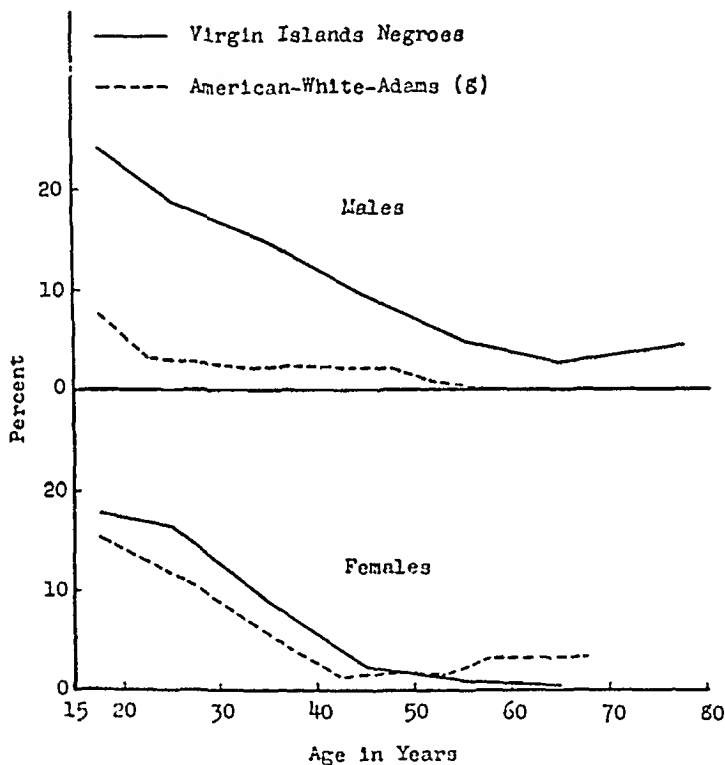


Fig. 3.—Percentage of males and females by age having systolic blood pressure of less than 110 mm. of mercury.

correlation in females. It appears that females tend to gain weight with age, but that males do not. The partial correlation coefficient of mean systolic blood pressure with age, with the weight constant, was 0.5022 for males and 0.7232 for females. The partial correlation coefficient of mean systolic blood pressure with weight, with the age constant, was 0.1281 for males and 0.1182 for females. From these calculations it is apparent that there is a fairly high degree of correlation of systolic blood pressure with increasing age and that this is not due to increasing weight.

Because a considerable proportion of the population was found to have syphilis, it was thought advisable to compare systolic pressure in negroes who had positive serologic reactions with those who had negative reactions. The mean systolic pressure for both males and females with





syphilis was appreciably higher than for those without syphilis, but, when the blood pressure was standardized for age, there was no significant difference. This is easily understood because both syphilis and systolic blood pressure increase with age, and the syphilitic subjects represented an older group in which higher blood pressure was to be expected.

TABLE V  
MEAN DIASTOLIC BLOOD PRESSURE OF NEGROES, BY SEX AND AGE

| AGE<br>(YEARS) | MALES |                   |                                    | FEMALES |                   |                                    |
|----------------|-------|-------------------|------------------------------------|---------|-------------------|------------------------------------|
|                | NO.   | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE | NO.     | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE |
| 15-19          | 240   | 72.45             | 11.39                              | 315     | 75.31             | 10.71                              |
| 20-24          | 268   | 76.40             | 11.02                              | 287     | 76.60             | 11.25                              |
| 25-29          | 223   | 80.65             | 13.34                              | 275     | 80.27             | 11.51                              |
| 30-34          | 155   | 81.80             | 13.91                              | 214     | 83.13             | 14.69                              |
| 35-39          | 144   | 84.35             | 15.42                              | 216     | 87.10             | 16.39                              |
| 40-44          | 121   | 87.60             | 17.37                              | 216     | 90.09             | 15.79                              |
| 45-49          | 139   | 90.30             | 17.69                              | 209     | 95.61             | 16.97                              |
| 50-54          | 133   | 90.70             | 16.73                              | 220     | 97.75             | 17.93                              |
| 55-59          | 134   | 92.20             | 20.68                              | 199     | 100.16            | 18.40                              |
| 60-64          | 125   | 93.50             | 20.19                              | 142     | 100.07            | 16.16                              |
| 65-69          | 80    | 90.20             | 17.35                              | 100     | 102.35            | 26.53                              |
| 70-74          | 39    | 95.30             | 19.51                              | 67      | 101.30            | 15.96                              |
| 75-79          | 25    | 94.90             | 17.08                              | 40      | 96.12             | 17.78                              |
| Over 80        | 17    | 97.50             | 25.02                              | 23      | 88.80             | 14.63                              |
| Total          | 1,843 | 84.05             | 17.25                              | 2,523   | 88.15             | 17.82                              |

TABLE VI  
MEAN DIASTOLIC BLOOD PRESSURE OF WHITE PERSONS, BY SEX AND AGE

| AGE<br>(YEARS) | MALES |                   |                                    | FEMALES |                   |                                    |
|----------------|-------|-------------------|------------------------------------|---------|-------------------|------------------------------------|
|                | NO.   | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE | NO.     | PRESSURE<br>(MM.) | STANDARD<br>DEVIATION<br>OF SAMPLE |
| 15-19          | 39    | 71.45             | 9.85                               | 22      | 73.87             | 13.38                              |
| 20-24          | 39    | 72.35             | 9.60                               | 30      | 74.84             | 9.38                               |
| 25-29          | 33    | 75.10             | 10.75                              | 28      | 75.36             | 9.10                               |
| 30-34          | 36    | 80.40             | 12.49                              | 33      | 77.35             | 8.65                               |
| 35-39          | 37    | 84.55             | 11.35                              | 23      | 80.55             | 11.21                              |
| 40-44          | 29    | 83.90             | 9.63                               | 24      | 79.80             | 9.35                               |
| 45-49          | 20    | 84.50             | 12.48                              | 30      | 82.17             | 10.08                              |
| 50-54          | 24    | 86.65             | 12.65                              | 17      | 86.02             | 14.11                              |
| 55-59          | 17    | 91.05             | 17.29                              | 14      | 95.85             | 13.82                              |
| 60-64          | 7     | 96.05             | 17.48                              | 19      | 85.39             | 14.99                              |
| 65-69          | 8     | 92.50             | 16.40                              |         |                   |                                    |
| Over 70        |       |                   |                                    | 8       | 95.00             | 14.74                              |
| Total          | 289   | 80.55             | 13.74                              | 249     | 80.29             | 12.12                              |

*Diastolic Blood Pressure.*—The results of our observations on diastolic blood pressure are given in Tables V and VI. These tables show that, in negroes, the pressure in females was significantly higher than in males, and that the pressure in whites was significantly lower than in negroes, with little difference between white males and females. In all groups there was an appreciable increase in pressure with advancing

age, but the rate of increase was less than that for mean systolic pressure. Fig. 1 shows this point graphically; the difference between the curves of systolic and diastolic pressure increases with age, indicating increasing pulse pressure.

#### DISCUSSION AND COMPARISON WITH OBSERVATIONS ELSEWHERE

There are clear-cut race and sex differences in mean blood pressure in the Virgin Islands. Negroes have a higher systolic and diastolic blood pressure than whites, and, among negroes, females have a higher pressure than males; the sex differences become apparent after the age of 35 years. In negroes there is a significant increase in systolic pressure with advancing age, but weight has little apparent effect. Much has been written about "normal" levels for blood pressure, and it is evident that what might be classed as normal for one population group would be considered as abnormal for another. Virgin Islands negroes have a high "normal" blood pressure as compared with standards in North America. In this discussion, normal is taken to mean that which is usual, regular, or most common, rather than that level of pressure, above or below which there is an excess morbidity and mortality.

Published observations on the average systolic pressure of men and women in the United States have been numerous and varied. We have selected for comparison two main classes: (1) observations upon persons who have been accepted as life insurance risks, and (2) observations upon a random group of persons attending a large clinic in a midwestern city, and upon a random group of private patients in New York City.

Symonds<sup>2</sup> analyzed the blood pressure of persons insured by the Mutual Life Insurance Company between 1907 and 1920. The systolic pressure of 150,000 men ranged from 121 mm. among those who were 15 to 19 years old to 135 mm. among those who were more than 60 years old. The average pressure of 12,000 women increased from 119 mm. to 135.5 mm. during the same life span. Hunter and Rogers<sup>4</sup> discussed blood pressure measurements made between 1913 and 1917 on 62,000 men and 5,000 women who were accepted as life insurance risks. Their observations were in essential agreement with those of Symonds, and showed that the average pressure of men increased from 120 mm. at 15 to 19 years of age to 134 mm. among those who were 55 to 59 years old, whereas the pressure of women increased during the same time from 117 mm. to 134 mm. Symonds' average systolic pressure for males of all ages was 125.3 mm., and, for females, 122.8 mm., which is a significant difference. Another group of life insurance examinees was discussed by Robinson and Bruce,<sup>5</sup> who analyzed measurements on 11,383 persons, all of whom had life insurance policies, and most of whom were urban dwellers of sedentary habits. In this group, 7,478 men showed a range in average pressure from 118 mm. in the 15 to 19 year group to about 134 for those

who were 60 to 69 years old. The average pressure of 3,405 women during the same span increased from 107 mm. to about 147 mm. The average for all men was 121 mm., and, for all women, 117 mm.

In the first two groups, the average systolic pressure was almost identical, age for age, but in the third group the pressure of the men was at a lower level, with a lower mean, and that of the women began at a considerably lower level in the early age groups, but increased to a higher level later, although the mean was considerably lower than for men, and much below that of the first two sets of life insurance figures. Persons who are able to buy life insurance policies are, of course, a highly selected group. In the first place, few of them belong to the lower economic levels, and, in the second place, persons with a known elevation of blood pressure will seldom be granted life insurance policies. Therefore, it is to be expected that mean blood pressure will average lower in such a group than in one which was not selected in this way. By comparison, both negroes and whites in the Virgin Islands had a higher mean systolic blood pressure in all except the younger age groups.

More nearly random groups were presented by MacNider<sup>6</sup> and Schwartz.<sup>7</sup> MacNider analyzed blood pressure measurements in a group of 5,540 persons who were seen in the University of Minnesota Hospital as outpatients or inpatients. They belonged to the lower or lower-middle classes of society and represented residents of both urban and rural areas; they included many who had no medical complaint, and the author felt they could be considered a fair random sample of the population. However, it is very likely that the group was not a true random sample, because it was composed of persons who sought medical advice at a hospital, and, as such, would be expected to include more than its share of ill people, and probably too many people with an abnormally high blood pressure. The systolic pressure of 2,282 men increased from 115.7 mm. among those who were 15 to 19 years old to 146.9 mm. in the 60 to 69 age group, and that of 3,258 women from 117.9 to 163.9 mm. in the same age range. The mean pressure was not given, but from his tables it is calculated as 123.2 mm. for males and 131.7 for females. The range of pressure was greater in this series than in the life insurance groups; both sexes started at lower levels in the younger groups, but rose to higher levels in the older groups; the greater range was among the females. The average for all ages for males was approximately the same as in Symonds's<sup>3</sup> series, but for females it was considerably higher. Schwartz<sup>7</sup> recorded observations on 5,800 private patients who consulted him over a ten-year period prior to 1940. The persons studied were mostly New Yorkers of sedentary habits, and it is probable that the majority had at least average incomes, for they were presumably able to pay for medical care. In this respect they doubtless were economically

better off than MacNider's<sup>6</sup> group, and were less active physically, for nearly all were urbanites, but otherwise they seem to be fairly comparable. In this series the systolic pressure of the men increased from 116.13 mm. between the ages of 11 and 20 years to 138.3 among those who were 61 to 70 years old; the increase among the women during the same span was from 110.78 to 157.61 mm. The ages were not quite comparable to MacNider's,<sup>6</sup> but the average pressure of both the men and women was lower for most ages. The mean, as computed from Schwartz' figures, is about 121.0 mm. for men and 129.0 mm. for women, which is only slightly lower than MacNider's averages. But in both these random series, although the average pressure was considerably higher than in the selected life insurance groups, it was still much lower than in Virgin Islands negroes and whites.

The proportion of Virgin Islands negroes with a systolic blood pressure of more than 150 mm., and the proportion with less than 110 mm., when compared with data from the United States, show marked differences. Adams,<sup>8</sup> using life insurance examiners' figures, showed that among men the percentage with a systolic blood pressure in excess of 150 mm. increased slowly from 0.6 at the ages of 15 to 19 years to 1.8 at 40 to 44 years, and more rapidly, thereafter, to a level of 21.0 at 60 to 64 years. Among females, the proportion was less than 1 per cent up to the age of 35 years, after which there was a steady increase to 33.3 per cent at 60 to 64 years. Among males the proportion below 110 mm. decreased from 7.6 at the ages of 15 to 19 years to zero at 55 years, whereas in females the proportion decreased from 15.3 per cent to about 1.5. MacNider's<sup>6</sup> figures showed a much higher proportion of persons with a systolic blood pressure above 150 mm. at all ages than those of Adams,<sup>8</sup> but were still lower than the Virgin Islands figures. It is apparent from Figs. 2 and 3 that, in Virgin Islands negroes, not only do a greater proportion of persons have a systolic pressure above 150 mm., but also that a greater proportion have pressures below 110 mm.

The mean diastolic pressure of Virgin Islands negroes is considerably higher at all ages than that of Virgin Islands whites, which, in turn, is above the mean in MacNider's<sup>6</sup> random sample in the United States; furthermore, Robinson and Bruce<sup>5</sup> showed that the mean was still lower in their group.

From the foregoing discussion certain things are evident: (1) Virgin Islands negroes have mean systolic and diastolic blood pressures which are much higher than those of persons in the United States; (2) the blood pressure of Virgin Islands whites is slightly higher than that of persons in the United States; (3) in both localities, after middle age, females have a higher blood pressure than males; and (4) a greater proportion of Virgin Islands negroes have both high and low blood pressure than do residents of the United States.

Can these differences be explained on the basis of race, climate, general economic level, or other environmental factors? The racial factor is probably important, because, in the Virgin Islands, the negro and white samples were comparable as to climatic environment, and, although the economic status of the whites may have been a little better than that of the negroes, the difference was not great. It is likely that the great majority of persons in the random samples studied by MacNider<sup>6</sup> and Schwartz<sup>7</sup> in the United States were white, which may explain why their blood pressure was lower than that of Virgin Islands negroes. There is some evidence that, in the United States, negroes have a higher blood pressure than whites. Adams,<sup>8</sup> who studied blood pressure in a group of white and colored workmen in the South, found that the average systolic pressure of 8,000 whites ranged from 117 mm. between the ages of 18 and 20 years to 139 mm. between 61 and 65, and, of 6,000 negroes, from 125 mm. to 148 mm. for the same ages. Dunn<sup>10</sup> stated that hypertensive heart disease occurs more frequently and is more severe in colored than in white women. On the other hand, Crile<sup>11</sup> stated that hypertension rarely occurs among primitive negroes, and Donnison<sup>12</sup> showed that, among 1,000 healthy, adult, male negroes in Kenya, in East Africa, the mean systolic pressure was very low; it increased from 123 mm. at the ages of 15 to 19 years to 126 mm. at 25 to 30 years and then decreased to about 106 mm. at the age of 60 years. Both Crile and Donnison believed that the "primitive" negro has a lower blood pressure than the "civilized" white person because the stress and strain of modern civilization have tended to produce hypertension. However, this is not a very logical explanation for the high blood pressure in the Virgin Islands, where most of the inhabitants are not much troubled by the stress and hurry of modern civilization. On the contrary, although they are poor and lacking in many things, they are, on the whole, quite contented, happy, and carefree. One must conclude that a racial difference actually accounts for higher blood pressure in negroes.

But, in addition to having more high blood pressures, the Virgin Islands negroes have more low blood pressures than the general population in the north. The excess of low blood pressure may be a result of climate and general environment. It is fairly generally agreed that blood pressure is lower in a tropical environment than it is in colder localities. Mason<sup>13</sup> showed that the average systolic blood pressure among white women dropped from 112 mm. to 107 mm. after they moved from a temperate to a tropical climate. Roddis and Cooper<sup>14</sup> showed that the systolic pressure of naval officers who were residing temporarily in the tropics was 10 to 12 mm. lower than would be considered normal in a temperate climate, and they concluded that blood pressure is modified by the effects of climate on physiologic activity. Saunders<sup>15</sup> ascribed the low average blood pressure in Yucatan partly to the tropical climate.

Among the negroes in the Virgin Islands there were many large, well-muscled, active laborers who appeared to be in perfect physical condition, with systolic blood pressures below 100 mm. It would seem, then, that at least two factors are active in determining the blood pressure level in the Virgin Islands, namely, race, which makes for higher pressure in negroes, and climate, which tends to lower pressure in all races.

It is interesting to speculate upon the effect economic factors may have upon blood pressure. The inhabitants of the Virgin Islands are generally poor; they suffer from vitamin deficiencies; and both negroes and whites have higher blood pressures than persons in the United States. In the United States, MacNider's random group had higher blood pressures than Schwartz' patients, who represented a higher economic level. It may be that lack of an adequate vitamin supply, partly as the result of poverty, will cause alterations in the vascular system which tend to increase blood pressure.

It is evident that sex influences blood pressure, for, in all the most nearly random samples, females have higher blood pressure than males. The pressure is about equal in the two sexes, or a little lower in females until they become 40 years old, after which it increases much more rapidly in females than in males, which suggests that a physiologic change at the menopause tends to increase blood pressure.

#### SUMMARY AND CONCLUSIONS

1. The average blood pressure of Virgin Islands negroes and whites is higher than that of residents of the United States.
2. Negroes had a higher average blood pressure than whites, both in the Virgin Islands and in the United States.
3. The systolic blood pressure of Virgin Islands negroes of both sexes increases significantly with age, but not with body weight.
4. Females have a significantly higher blood pressure than males; this difference becomes increasingly evident after the age of 35 years.
5. A greater percentage of negroes in the Virgin Islands have a systolic blood pressure of more than 150 mm., and of less than 110 mm., than residents of the United States.
6. A tropical climate may exert a depressing effect upon blood pressure.
7. Poverty, with its associated vitamin deficiencies, may tend to raise blood pressure.

We wish to thank the many persons who assisted with the observations discussed in this paper. Dr. Knud Knud-Hansen, commissioner of health for the Virgin Islands, who allowed the studies to be made in the Virgin Islands, gave freely of his own time and advice. Dr. Meredith Hoskins, Chief Municipal Physician of St. Croix, Dr. John Moorhead and Dr. Norman Sloan, formerly municipal physicians in St. Thomas and St. Croix, Dr. Walter Corey, of the United States Public Health Service, and Dr. Ricardo Guinto all gave valuable help during the clinic examinations.

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## A NEW TYPE OF ELECTRODE FOR ELECTROCARDIOGRAPHY

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IN THE electrocardiographic or cardioscopic examination of large numbers of patients in dispensary or hospital, considerable time is consumed in attaching and removing the electrodes. A new type of electrode, which has been devised in the outpatient department of the

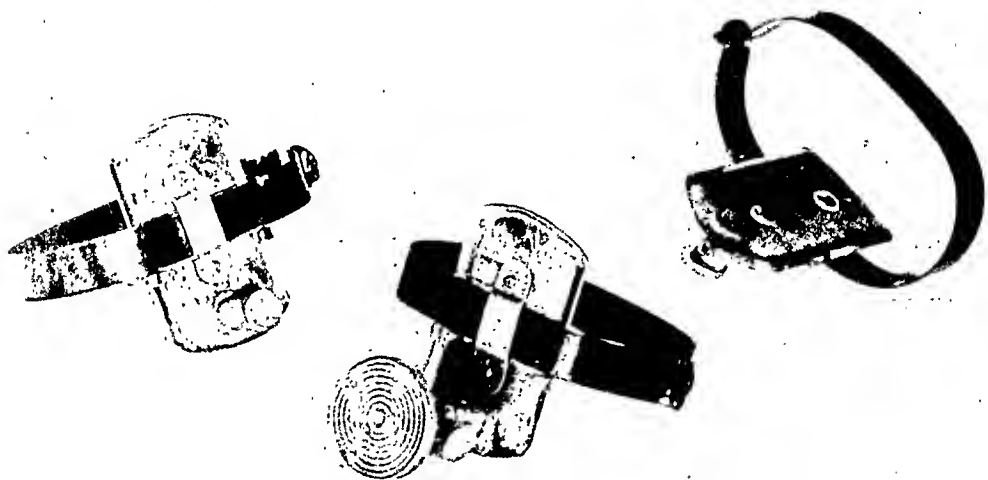


Fig. 1.—Clips as applied to conventional electrodes.

Johns Hopkins Hospital, may be applied and removed much more rapidly than the usual types. These electrodes are constructed by attaching ordinary bicycle clips to the conventional electrodes by means of a thin metal bridge, as shown in Fig. 1. The clip is so mounted as to permit limited motion of the electrode along the side. A round metal disc, about  $1\frac{3}{8}$  inches in diameter, is joined to the upper surface of the right arm electrode, thus making it unnecessary to disconnect the wire from the right arm electrode and to connect it again to a chest electrode for chest leads. The right arm electrode is easily slipped off the arm, and the metal disc is applied to the precordium; the reversal of current from left leg to chest is accomplished through the electrocardiograph itself.

From the Cardiographic Laboratory, the Johns Hopkins Hospital and Medical School.

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We have noted no appreciable increase in the tendency of the beam or string of the electrocardiograph to "float" because of the use of dissimilar metals. The electrodes may be used with either string or vacuum tube electrocardiographs.

The electrodes, as described, fit most arms and legs. For patients with small, thin arms and legs, a small sponge rubber pad may be used under the bicycle clips to secure a firmer connection.

## Department of Clinical Reports

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### LEIOMYOMA OF THE PERICARDIUM

#### REPORT OF A CASE

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PRIMARY tumor of the heart or pericardium is so unusual that reports of cases are desirable and interesting. This communication undertakes to present a case of leiomyoma of the pericardium, which is, as far as can be ascertained, the second such case on record, and also to cite briefly recent similar reports.

The entire field of tumors of the heart was reviewed by Yater,<sup>1</sup> in 1931. At that time he found reference to the following pericardial neoplasms: sarcoma, lipoma, polyp, fibroma, phlebogenous angioma, carcinoma (or endothelioma), teratoma, and neurofibroma. He stated that he himself had seen a cyst.

Since 1931, eighteen additional cases of pericardial tumor have been described; the reports of sixteen of these are available. These include lipoma,<sup>2</sup> neurofibroma,<sup>3</sup> leiomyofibroma,<sup>4</sup> fibroma,<sup>5</sup> angioma,<sup>6</sup> teratoma,<sup>7-9</sup> malignant hemangioblastoma,<sup>10</sup> endothelioma,<sup>11, 12</sup> and sarcoma.<sup>13-17</sup>

Since the clinical manifestations in cases of benign tumor vary little from those of malignant tumors, the two may be considered together. The complaints of eleven of these sixteen patients suggested disease of the heart (dyspnea, pain, fatigue, venous congestion).<sup>2, 3, 8-10, 12, 17</sup> Four patients died suddenly; one was a child under treatment for tuberculosis,<sup>4</sup> and another was an infant with pemphigus.<sup>6</sup>

Data upon physical signs are available in twelve cases. Enlargement of the heart was noted in nine.<sup>2-4, 8-10, 14, 16, 17</sup> Of the remainder, one patient presented signs of pericardial effusion,<sup>12</sup> and one had a pericardial friction rub.<sup>15</sup> Bloody fluid was obtained upon pericardial paracentesis in one case,<sup>10</sup> and bloody fluid upon thoracentesis in another.<sup>16</sup>

Roentgenologic examination was made in eleven cases. Generalized enlargement of the heart was described in four;<sup>2, 4, 10, 17</sup> pericardial

From The Roosevelt Hospital, New York.  
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effusion, in one;<sup>12</sup> and localized or bizarre projections from the cardiac silhouette, in seven.<sup>2, 3, 8, 9, 13, 11, 16</sup>

Electrocardiograms were taken in six cases. One tracing exhibited left axis deviation only.<sup>12</sup> All of the remaining five were definitely abnormal, i.e., four showed nonspecific T-wave changes;<sup>14-17</sup> three showed disturbances of rhythm;<sup>9, 14, 16</sup> and one showed slurring of the QRS complex.<sup>17</sup> No instance of changes similar to those described by Vander Veer and Norris<sup>18</sup> as characteristic of subpericardial myocarditis was observed.

A clinical diagnosis of tumor was made in one case.<sup>13</sup> The validity of this diagnosis must remain open to question, for it is the only case in the group in which no autopsy was performed. The existence of neoplasm within the mediastinum was recognized once.<sup>16</sup>

From the foregoing it will be seen that tumor of the pericardium is rare, that it may either attract attention to itself or cause sudden death, and that roentgenologic abnormalities are the most suggestive evidence of its presence.

#### REPORT OF CASE

W. M., a white American boy, aged 19 years, was admitted to The Roosevelt Hospital July 1, 1939, at 6 P.M. While playing baseball a short time before, he had been seized with a pain in his chest which he thought was due to indigestion. He located the pain behind the lower half of the sternum. He had gone home and taken rhubarb and soda, but obtained no relief, and therefore had come to the hospital.

He stated that he had been in another hospital about six months previously because of a similar pain and that he had been treated for "pericarditis." Subsequently he had been to a clinic where he was told that he had "something wrong with his heart." About two months before his admission to The Roosevelt Hospital he had had a brief attack of the pain, but this had passed off when he took rhubarb and soda. Aside from these attacks, he said that he had always enjoyed good health.

Physical examination showed a well-developed youth who did not appear to be ill. There was no fever. The blood pressure was 120/95.

The positive signs were confined to the heart. On inspection, a definite systolic impulse was seen in the third left intercostal space, just beyond the sternum. Percussion revealed marked widening of mediastinal dullness to the left in the second and third intercostal spaces. There was a loud systolic murmur at the apex.

There was a moderate polymorphonuclear leucocytosis. A roentgenogram of the chest in the anteroposterior position showed a large, smooth, rounded projection occupying the position of the transverse and descending aorta (Fig. 1).

During the night the patient began to vomit, and this symptom continued obstinately despite hypodermics of codeine. In the morning, except for the vomiting, the picture remained essentially unchanged. Because of loss of fluids, an infusion of 10 per cent glucose in saline was given. It was noted at once that the inflow of the fluid was abnormally slow for the technique employed.

About noon, toward the end of the infusion, the patient began to retch more violently than ever, and became cyanotic, after which he had an epileptiform convulsion which lasted several minutes. The infusion was immediately discontinued.

The situation was now rapidly reappraised, and the following points seemed salient. The arterial blood pressure had fallen to 90/60; the venous pressure was high (witness the slow inflow of the infusion); the area of absolute cardiac dullness equaled that of the relative cardiac dullness; and the femoral pulses were equal. Because of these facts, a diagnosis of acute compression of the heart was made;<sup>19</sup> the weight of the evidence favored sudden effusion as the cause. Rupture of a dissecting aneurysm of the aorta into the sac was considered, in view of the percussion and roentgenographic outlines, but the previous history of pericarditis favored the former hypothesis, and the equality of the femoral pulses seemed evidence against the latter. Since it was apparent that immediate action was essential, pericardial paracentesis was decided upon and carried out forthwith.



Fig. 1.—Roentgenogram which clearly demonstrates the enlarged heart and bulge of the pericardium, especially over the base.

After the skin was anesthetized with procaine hydrochloride, a needle was inserted into the third left intercostal space within the nipple line and gently introduced to a total depth of 5 cm., constant suction being made. No more than a drop or two of blood was obtained, and no motion of the heart was felt.

At this point, the patient's mother arrived at the hospital for the first time and gave additional information about the case. She stated that she had been told at one of the institutions which he had previously attended that he had "a tumor in his chest," and that he had received roentgen therapy. In the light of

this information the possibility of hemorrhage into a cellular tumor was considered, but, since the patient's condition would not permit taking lateral and oblique roentgenograms, it could not be investigated further. He was given morphine, ouabain, and oxygen on the theory that his one chance lay in conservative management. Despite these measures his cardiac failure became progressively worse, and he died at 6 o'clock the following morning, thirty-six hours after admission to the hospital.

The final clinical diagnosis was dissecting aneurysm of the thoracic aorta.



Fig. 2.—Photograph of the heart with the left ventricle open, exposing aortic valve and mitral leaflet. The tumor is broken up somewhat but is adherent to the parietal pericardium.

*Pathologic Observations.*—At autopsy, three hours post mortem, there was cyanosis of the skin, conjunctivae, mucosae, and fingernails. Three needle puncture marks were found in the left third intercostal space, 3 cm. to the left of the midline. There were petechiae in the gastric mucosa, generalized venous congestion, and enlargement of the liver.

The pericardial sac measured 15 cm. in width at the base. The apex of the heart was partially obscured on its anterior aspect. In the upper area, over the left auricle and base anteriorly, a definite bulge of the pericardium was evident. This area was tense, and, when incised, allowed the escape of about 60 c.c. of fluid blood which contained shreds of friable, grayish tissue. The parietal pericardium was displaced outward by a large tumor mass in this area (Fig. 2). Over the apex and posterior surface the pericardial space was obliterated by fibrous adhesions, some of which were bloodstained. A line of cleavage could be followed between the tumor mass and the myocardium. The ventricular and auricular muscle was free from involvement on gross inspection. The left auricular cavity

was of small size, apparently because of pressure by the tumor mass. The cusps of the mitral valve were slightly thickened. Their surfaces were smooth. The chordae tendineae were smooth and thin. The endocardial surfaces were smooth throughout. The other valves were not unusual.

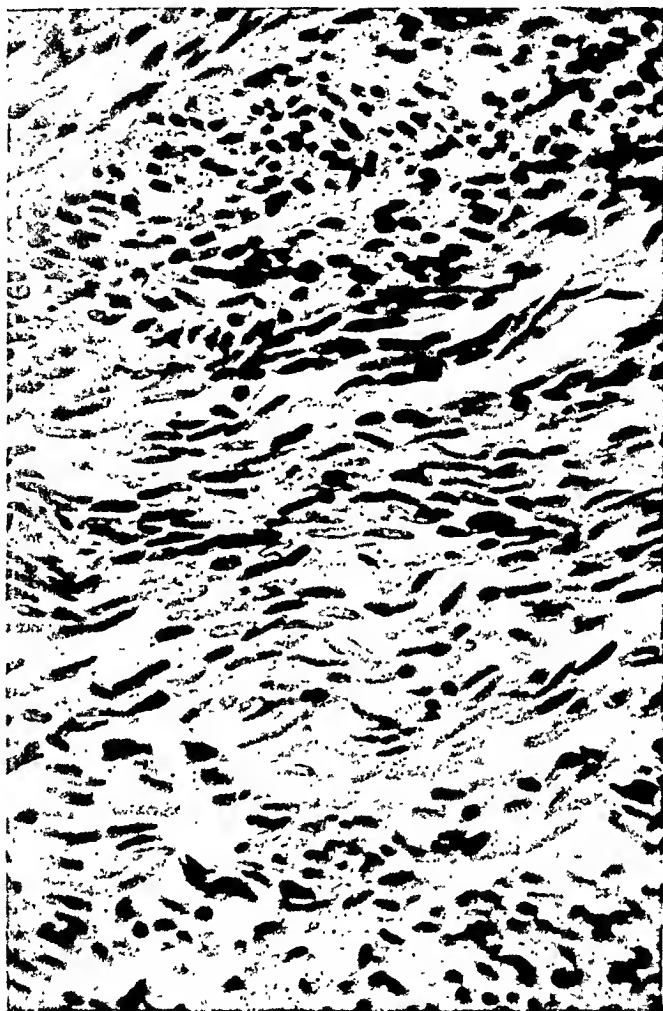


Fig. 3.—Photomicrograph of a hematoxylin and eosin stained section of the tumor. Elongated, slender nuclei, with blunt ends are evident. Cytoplasm is faintly visible. ( $\times 720$ .)

Microscopic examination of the tumor revealed uniform-appearing, elongated cells, with long, slender nuclei. Most of the nuclei had blunt ends (Figs. 3 and 4). Some of the nuclei were twisted. The nuclear chromatin was evenly distributed. Nucleoli, when present, were small. A few larger nuclei were dark. Mitotic figures were rarely seen. The cytoplasm was not well stained, but, when seen, was acidophilic. Some cells revealed ribbonlike bands of cytoplasm. The phosphotungstic acid hematoxylin stain revealed no cross striations. The cytoplasm showed bluish, longitudinal streaks, or threads, in some cells, which were suggestive of myofibrillae. The cells were arranged in bundles, coursed in various planes, and were consequently cut at various angles.

The stroma was present in small amounts. Blood vessels were fairly numerous, all of them with well-formed walls. Many of the vessels were dilated and distended with blood. Small hemorrhages were frequent in some areas.

The gross appearance suggested a tumor of the pericardium in which recent hemorrhage had occurred. Older, smaller hemorrhages probably accounted for the fibrous obliteration of the other portions of the pericardial space. Microscopically, the uniformity of the cells, which showed but slight variation in size and shape, and the absence of invasion of the surrounding tissues or the myocardium strongly suggested that this was a benign tumor of the pericardium. The elongated cells, with, at times, wide bands of cytoplasm and elongated nuclei with blunt ends, are evidence that it was a tumor of smooth muscle origin. As such, it might have arisen from blood vessels somewhere in the pericardium, although it was not possible to ascertain the exact point of origin.

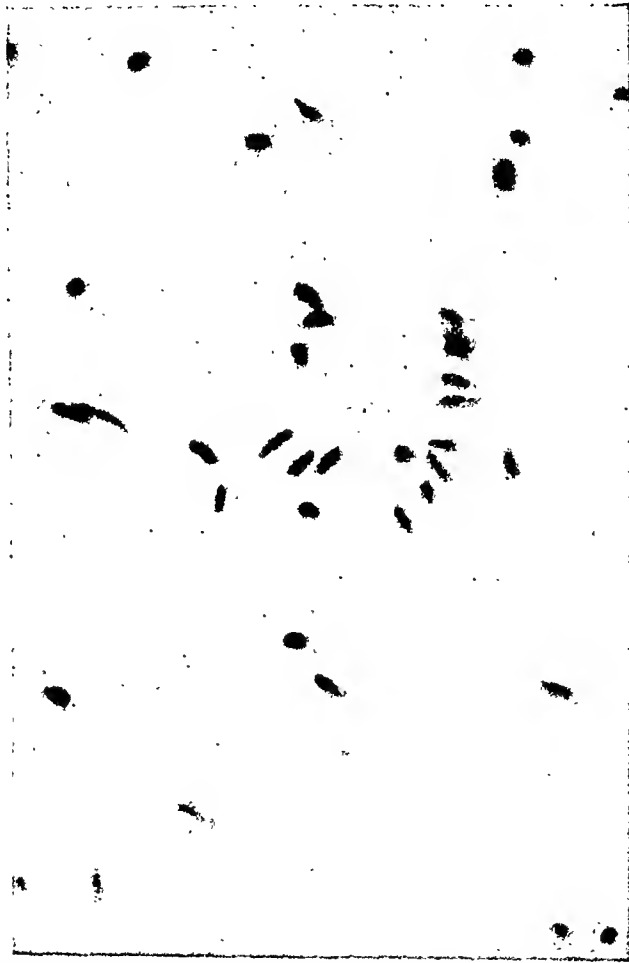


Fig. 4.—Touch preparation of the tumor mass. Rather long, narrow, cytoplasmic bands are clearly demonstrated. ( $\times 1500$ )

#### COMMENT

Our case appears to be the second recorded instance of leiomyoma of the pericardium; the previous instance was that of Kaplan.<sup>4</sup> The tumor in Kaplan's case was more solid, had a demonstrable origin in the left pulmonary vein, and had not been the site of hemorrhage.

As in the majority of other cases of pericardial tumor, the history, physical signs, and roentgenologic observations attracted attention to the



heart as the site of disease. Like the majority of other observers, we misinterpreted the evidence and arrived at an erroneous diagnosis.

From the pathologic point of view, the cause of death was probably compression of the auricles by the tumor; this compression was suddenly increased by the hemorrhage. Bleeding was doubtless brought on by the patient's exertion when playing baseball.

The case is reported because of its intrinsic interest and as a reminder that, although extremely rare, tumor of the pericardium does occur and should be considered as a diagnostic possibility in the presence of a bizarre clinical picture of heart disease.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: I. Immediate Prognosis. *Arch. Int. Med.* 68: 913, 1941.

It can be stated that the immediate outlook in a case of acute coronary thrombosis is extremely difficult to predict. Although many of the clinical and electrocardiographic features analyzed may indicate that the condition is either more or less critical, there is practically no criterion which is infallible. However, weighing all the information available together with the general appearance of the patient enables the physician to make a fair estimate as to the immediate prognosis.

AUTHORS.

Hedley, O. F.: Facilities in the United States for the Special Care of Children With Rheumatic Heart Disease. *Pub. Health Rep.* 56: 2321, 1941.

There were in the United States at the beginning of 1940 one rheumatic heart disease hospital, seven convalescent institutions of various types devoted exclusively to the treatment of children with heart disease, and one organization with a unit furnishing foster home care to children recovering from rheumatic infection. One of the convalescent sanatoriums is adding facilities for the care of essentially hospital cases. Since the beginning of 1940 at least two other rheumatic heart disease sanatoriums have been opened, while beginning in the fall of 1940 a general convalescent institution in Florida was to be devoted entirely to the treatment of rheumatic heart disease.

There are a number of convalescent sanatoriums which furnish care to rheumatic cardiac patients. Although some of them have wards set aside for these patients, in many instances they do not furnish care on a large scale. In most places, additional beds allocated to this purpose would be sufficient.

AUTHOR.

Trotter, W. R., and Eden, K. C.: Total Thyroidectomy for Heart Failure. *Brit. Heart J.* 3: 200, 1941.

A case has been described in which the complete removal of a normal thyroid gland was followed by the disappearance of auricular fibrillation and congestive cardiac failure. Auricular fibrillation reappeared when the patient was given 1.5 gr. of thyroid extract daily but disappeared again when the dose was reduced to 0.5 gr. daily.

It is suggested that in this case the normal thyroid hormone had the same effect on the heart as has the excessive or abnormal secretion in cases of thyrotoxicosis.

It is suggested that cases of auricular fibrillation or flutter, in which the disorder of rhythm is either paroxysmal or of short duration and in which there is no evidence of structural damage to the heart, might be expected to benefit in a similar way as the result of total thyroidectomy.

AUTHORS.

Baggenstoss, A. H., and Barker, N. W.: **Unilateral Renal Atrophy Associated With Hypertension.** *Arch. Path.* 32: 966, 1941.

The incidence of hypertension was determined in eighty-four cases of unilateral renal atrophy and thirteen cases of unilateral renal hypoplasia. There were forty-eight cases of pyelonephritic atrophy, twenty-eight of hydronephrotic atrophy, and eight of pyonephrotic atrophy. Death in most of these cases was due to neoplastic disease or infections of various types. Hypertension was a cause of death in only five cases. Only in the groups of cases of pyelonephritic atrophy (39.6 per cent) and the group of cases of pyonephrotic atrophy (37.5 per cent) was the incidence of hypertension greater than in the control group (29 per cent). The incidence of hypertension was 41.9 per cent for the group of cases of pyelonephritic atrophy in which the atrophied kidney weighed 75 Gm. or less and 35.4 per cent for the group in which the atrophied kidney weighed more than 75 Gm.

In twenty of the forty-eight cases of pyelonephritic atrophy and in twelve of twenty-five cases of hydronephrotic atrophy there was some degree of active inflammation in the opposite kidney. Inflammation in the opposite kidney was present more often in cases in which hypertension was a feature than in those in which it was not observed.

The degree of arteriosclerosis in the opposite nonatrophic kidney was generally less severe than that in the atrophied kidney. In eight of nineteen cases of pyelonephritic atrophy associated with hypertension, the blood vessels were considered normal for the age of the patient.

The results, although of questionable statistical significance because of the small number of cases, suggest that unilateral pyelonephritic atrophy is more often associated with hypertension than would be expected on the basis of chance. They also suggest that hypertension is more likely to be present if the degree of atrophy is severe. As abnormal vascular changes had not occurred in the opposite nonatrophic kidney in a number of cases of unilateral renal atrophy associated with hypertension, it is suggested that in many cases in which hypertension is in an early or mild stage it may not be associated with renal arteriosclerosis.

AUTHORS.

Oksanen, A. J., Nylander, P. E. A., and Vesa, A.: **Concerning the Question of Puerperal Embolism of the Arteries.** *Acta Soc. med. fenn. duodecim* (fase 3) 27: 1941.

Although embolism of the peripheral arteries, as a disturbance during puerperium, is a most uncommon occurrence, it is not without clinical importance. More often than not diagnosis has been made at a very late stadium, for which reason it is possible that the prognosis of the cases appears to be bad. Operative embolectomy has been performed in a surprisingly small number of these cases and should, in the authors' opinion, be worthy of notice in obstetric circles. The authors describe a case of a 29-year-old woman who, on the fourteenth day after her confinement, which had been accompanied by a puerperal fever, showed symptoms which pointed to embolism of the femoral artery. Large quantities of narcotics were not used, and the embolectomy was performed operatively shortly after. The

operated leg healed completely. When the patient's heart was examined, signs of myocarditis were found, and the authors drew their conclusions from this that the embolus originated from the mitral valve or from some part of the thrombotic matter on the surface of the endocardium of the left side of the heart. The authors analyze the indications for operation and refer to the literature dealing with this subject.

AUTHORS.

**Snellman, A.:** Contribution to the Clinique of Genuine Basal Cerebroarterial Aneurysms. *Acta Soc. med. fenn. duodecim* (fase 3) 27: 1941.

The author reports eight cases of genuine aneurysm in the region of the anterior portion of the *circulus arteriosus willisii*, exposed by arteriography and observed by him at the Finnish Red Cross Hospital in Helsinki. In three of these cases aneurysm occurred in the supraclinoid part of the *carotis interna*, in one case in the *arteria communicans anterior* (?), in one case in the *arteria cerebri anterior*, and in three cases in the basal portion of the *arteria cerebri media*.

From these cases the author believes that it is possible to set up certain clinical types, which are grouped as follows: (1) Apoplectic, violent, lethal cerebral aneurysm; (2) apoplectic, lethal or nonlethal, as well as recidivating cerebral aneurysm (a) with symptoms of abolition from various regions in the cerebral hemisphere or (b) without symptoms of abolition; and (3) cerebral aneurysm with typical or less typical cavernosus syndrome (ophthalmoplegie migraine).

Conservative treatment was used in four of these cases, and surgical therapy, in four. Extracranial carotis ligature was applied in three cases (ophthalmoplegie migraine with aneurysm in the supraclinoid portion of the *carotis interna* in one case, partial hemiplegia and disturbances of speech with aneurysm in the first part of the *arteria cerebri media* in one case, and abducens paralysis and aneurysm in the first part of the *arteria cerebri anterior* in one case. The indication for an application of carotis ligature was different in each one of the cases. The first two mentioned cases recovered without appearance of any cerebral symptoms; in the third case massive hemiplegia and aphasia ensued by the end of the second day, probably as a consequence of secondary thrombosis.

An extensive, subcortical accumulation of blood was removed in one case.

In connection with these cases the author expresses his views on the possibilities of surgical treatment in the aneurysms in question.

The author discusses the etiological viewpoints, and he feels inclined to emphasize the significance of congenital predisposition in some of the cases.

AUTHOR.

**Nylander, P. E. A.:** Concerning the Question of Thrombosis in the Inferior Vena Cava. *Acta Soc. med. fenn. duodecim* (fase 3) 27: 1941.

The author describes an interesting case of a patient whom he has had under observation for seven years. The patient, a 9-year-old boy, was suffering from acute osteomyelitis of the *os ilii* in which a complication arose in the form of a thrombus in the vena cava. Blocking of the veins led to the formation of a superficial anastomatic network stretching from the upper part of the thigh to the mammary regions, and the superficial veins remained. The child's development continued normally. The action of the heart, at a later examination, was regular; roentgenograms and electrocardiograms showed no deviation from the normal. The author deals briefly with the literature on the subject, taking into consideration the possible indications for operation.

AUTHOR.

Fauteux, M.: Experimental Study of the Surgical Treatment of Coronary Disease  
Surg., Gynec. & Obst. 71: 151, 1940.

It has been suggested that the similarity of arteriosclerotic disease of the coronary arteries and of the extremities should permit of the application in the heart of surgical methods found useful in the treatment of peripheral vascular disease. Experiments on dogs are described in which were performed (a) partial coronary arteriectomy of the ramus descendens and (b) partial coronary arteriectomy of the same arterial trunk combined with ligation of the vena cordis magna.

When a partial resection of the ramus descendens at a high level was done, a high mortality resulted. When the same procedure was carried out after venous ligation, all dogs, except those dying of operative complications and intercurrent diseases, remained healthy for more than one year.

It is concluded that vena cordis magna ligation in occlusion of the left ramus descendens helps to maintain adequate coronary circulation after partial coronary arteriectomy.

The results of these experiments suggest that in cases properly selected coronary vein ligation may be expected to act as a preventive measure against a second attack of coronary thrombosis and also to improve the coronary circulation sufficiently to relieve the pain of "angina of effort."

Furthermore it seems a logical procedure in traumatic surgery of the heart whenever it is necessary to ligate an important coronary arterial branch that is bleeding.

AUTHOR.

Atlas, L. N.: The Role of the Second Thoracic Spinal Segment in the Preganglionic Sympathetic Innervation of the Human Hand—Surgical Implications. Ann. Surg. 114: 456, 1941.

Through a peculiar operative error, an opportunity was presented to perform a controlled study on the contribution of the second thoracic spinal segment in the sympathetic innervation of the human hand. The reported case shows that the second thoracic spinal segment definitely plays an important part in the preganglionic sympathetic innervation of the hand.

Any operation designed to denervate preganglionically the blood vessels of an arm must destroy completely all white rami from the second thoracic spinal segment. In every instance, as determined by skin temperature and sweat distribution studies, complete, immediate denervation of the blood vessels and sweat glands of the upper extremity and the cutaneous vessels and sweat glands of the corresponding half of the face should be obtained. In none should a Horner's syndrome ensue.

AUTHOR.

Gebauer, P. W., and Nichol, A. D. Ligation of the Patent Ductus Arteriosus. Ohio State M. J. 37: 538, 1941.

Experiences with three cases of patent ductus arteriosus in patients between 11 and 39 years of age are presented. From these patients and from a study of the literature the following tentative conclusions are made.

The authors believe that operation should be performed early because children withstand thoracic surgical procedures so much better than do adults, because the operation is technically easier, and because the shorter the duration of patency the less the degree of pulmonary dilatation, cardiac enlargement, vessel sclerosis, and the less severe the postoperative reaction. Early intervention should be preceded by a period of observation during which diagnostic studies are made, and which is long enough to preclude the rarity of spontaneous closure.

Patients are often urged to lead an inactive life during childhood, may be forced to inactivity by a diminished cardiac reserve in early adulthood, and throughout life are distinctly more susceptible to bacterial endocarditis, aneurysm and rupture of the ductus, or thrombus formation as well as rapid or slow cardiac failure. In some instances, middle life may be reached comfortably. Such instances are rather rare inasmuch as Abbott found the mean age of ninety-two patients to be 24 years at the time of death. On the other hand, the risk of operation is much greater in adults near the limit of their cardiac reserve. The operation may be most difficult because of sclerosis, or because the ductus finally becomes nothing but adjacent holes in the wall of two large vessels. Exploration should be undertaken most cautiously in later life, and in some instances the physician should abandon it rather than attempt to dissect around something which has ceased to exist.

AUTHORS.

Harris, R. I.: **Obliterative Vascular Disease: Treatment by Sympathectomy.**  
Canad. M. A. J. 45: 529, 1941.

The two obliterative vascular diseases commonly observed are Buerger's disease and peripheral arteriosclerosis.

Although the pathologic changes are profoundly different in the two diseases, the result in each case is an intermittently progressive slowing of the circulation which manifests itself by a distinctive clinical picture.

Many cases of either disease have an associated degree of vasospasm which contributes materially to the diminished blood flow. The degree of this vasospasm can be measured by preoperative tests, such as spinal anesthesia and the Landis test.

In all severe cases of Buerger's disease and in selected cases of severe peripheral arteriosclerosis the operation of sympathectomy should be given serious consideration. If the preoperative tests result in a rise in skin temperature of 3° C. or more, a beneficial result from operation can be assured. Even a lower rise in skin temperature does not entirely preclude the possibility of improvement sufficiently great to justify the procedure.

AUTHOR.

Welch, C. E., and Faxon, H. H.: **Thrombophlebitis and Pulmonary Embolism.**  
J. A. M. A. 117: 1502, 1941.

The authors believe that the immediate decision to be made in any given case of thrombophlebitis is whether the patient should be treated conservatively or by ligation of the vein. If conservative therapy is employed, lumbar injection of procaine hydrochloride should be done if vasospasm is considerable. If the deep venous channels are interrupted, heparin is often of value when administered post-operatively. It must be emphasized that these concepts may be modified greatly as our experience increases. The important fact is that thrombophlebitis is no longer observed passively but is now accepted as a disease that must be treated vigorously.

AUTHORS.

Woods, W. W., and Peet, M. M.: **The Surgical Treatment of Hypertension. II. Comparison of Mortality Following Operation With That of the Wagener-Keith Medically Treated Control Series.** J. A. M. A. 117: 1508, 1941.

The prognosis of patients with a high level of blood pressure and angio-pastic changes of the retinal arterioles is much more favorable following operation than following medical treatment.

The surgical treatment of patients with malignant hypertension has resulted in a survival of 33 per cent after five years, whereas following medical treatment in the control series the mortality was more than 99 per cent.

In general, a favorable prognosis following operation seems to depend on a minimal degree of retinal arteriolar sclerosis rather than on the level of blood pressure, or the absence of retinitis with hemorrhages and exudates, or papilledema.

AUTHORS.

Field, H., Hoobler, S. W., and Avery, N. L.: Results of Chemotherapy in Subacute Bacterial Endocarditis. *Am. J. M. Sc.* 202: 798, 1941.

Among thirty-six cases of subacute bacterial endocarditis treated with sulfonamide drugs there were five cases with one or more probably falsely negative blood cultures, three instances of probable sterilization of the blood stream with normal temperature temporarily, and one cure of a probably proved case. Among the five patients who also received continuous intravenous infusion of heparin there was one death with cerebral hemorrhage and no cure.

The reported experiences in the chemotherapy of subacute bacterial endocarditis warrant persistence in the accumulation of data concerning the different adjuncts to chemotherapy and the selection of a sulfonamide drug on the basis of bacteriostasis, demonstrable in vitro, for the strain of organism obtained from the individual case.

AUTHORS.

Wilkerson, F.: Functional Cardiac Disorders. *J. M. A. Alabama* 11: 45, 1941.

The important essentials in the treatment of functional cardiac disorders are, (1) a thorough examination and (2) the proper approach with constantly repeated words of encouragement and reassurance. Faithful following of these ideals will give comfort to a large class of sufferers who, all too frequently, fail to get the help to which they are entitled.

AUTHOR.

## Book Review

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TREATMENT OF THE PATIENT PAST FIFTY: By Ernst P. Boas, M.D., Assistant Clinical Professor of Medicine, Columbia University. The Year Book Publishers, Inc., Chicago, 1941, 308 pages, 19 illustrations, \$4.00.

Nearly half of the pages of this book are devoted to discussion of the cardiovascular diseases. It is apparent that the author is an authority in this field, and it is believed that any practitioner who reads the book would thereby increase his knowledge of heart disease. The material presented is extensive, and considerable space is given to pathologic and diagnostic problems, as well as to treatment. The style of writing tends toward abruptness, with frequent short statements of fact. On debatable points there is a lack of discussion, an omission which may have been purposeful; the author is content to formulate and present his own medical creed. The pages abound in general truths and useful advice, but occasional didactic statements undoubtedly will stimulate the argumentative reader to question whether certain ideas have been established as facts. There is a minimum of references to the literature; this does not detract from the book except when some disputable opinion has been voiced. A few examples of sentences with which the reviewer takes issue are: "Headache suggests the probability of death from apoplexy" (in hypertension). "Potassium sulfocyanate causes such distressing side reactions it should not be used" (in hypertension). "I have a patient who had chancre at the age of twenty and who first developed syphilitic aortitis at age fifty-eight" (syphilitic heart disease). "After the age of sixty, one encounters occasional cases of arteriosclerotic mitral stenosis" (valvular disease). "Airplane flights not exceeding 14,000 feet are not injurious to the heart by reason of the high altitude" (for any continued airplane flight the reviewer believes the oxygen tension is inadequate at more than 10,000 to 12,000 feet for patients who have advanced coronary arteriosclerosis).

It is believed that, although the specialist in the cardiovascular diseases will be disappointed in what he acquires from this book, the general practitioner should find it of some value as a helpful guide in the management of the aging patient. Perhaps certain points which have been mentioned in the book might have been described at greater length, for instance, calcareous aortic stenosis. Arteriosclerosis as a general topic has not been presented in any detail, and this may well reflect realization that there is so much yet to be learned concerning it. The value of salyrgan in the absence of evident edema perhaps has not been adequately discussed. The book much resembles a general synopsis of medicine, and therefore somewhat belies its title. Whether or not the treatment of a patient more than 50 years old is sufficiently different from the treatment of a patient less than 50 years old to justify an entire book on the subject is something about which each physician must form his own opinion.

H. B. BURCHELL.



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A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

\*Executive Committee.

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## Original Communications

### EFFECTS OF PHYSICAL STRAIN AND HIGH ALTITUDES ON THE HEART AND CIRCULATION

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CAMBRIDGE, MASS.

IT IS with some hesitation that I address this group of experts on cardiac function on such a subject as that assigned to me. I am not a physician nor can I speak authoritatively about one of your principal tools, the electrocardiograph. Despite these limitations I am encouraged to come before you by two facts. First, despite the rapid advances in cardiology in recent years, there remain wide gaps in our knowledge of cardiac function in healthy human beings. One of these has been narrowed by my good friend Ashton Graybiel at this meeting; he has discovered unexpectedly large variations in the electrocardiograms of several hundred healthy students and flying cadets. Second, working with many associates in the Harvard Fatigue Laboratory, and, in recent months, in the Aero Medical Research Unit at Wright Field, I have learned much about the cardiovascular response to exercise and to high altitudes. I propose to discuss some recent observations regarding the dependence of cardiovascular responses to moderate and severe exercise on age, training, race, and environmental conditions.

The measures of cardiovascular function which were used include the heart rate, the total oxygen uptake, a derived function, the "oxygen pulse," and the cardiac output. The total oxygen intake during maximal work is perhaps the best functional test of cardiorespiratory performance. It depends upon the volume of air supplied to the lungs, on conditions controlling diffusion in the lungs, on the rate of blood flow, and on the oxygen content and carrying capacity of venous blood. The "oxygen pulse" is derived from the first two functions; it amounts to the oxygen delivered to the tissues per beat of the heart. The cardiac

\*The Lewis A. Conner lecture, delivered at the seventeenth scientific session of the American Heart Association, Cleveland, May 30, 1941.

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output in man is best measured by the acetylene method of Grollman.<sup>1</sup> In the dog it may be estimated directly by puncture of an artery and of the right side of the heart, and ascertaining the oxygen content of each sample and also the oxygen consumption of the animal. Unfortunately, neither of these methods is satisfactory during maximal exercise.

Cardiovascular responses to moderate exercise have a notable dependence on age. We have studied the performance of a large number of subjects doing a fixed task on the treadmill, i.e., walking at 5.6 km. per hour up a grade of 8.6 per cent. This can be accomplished by boys of 6 years or men of 70. The oxygen consumption is about seven times the basal rate. The heart rate after fifteen minutes of such work is much higher in boys than in men of middle age. Robinson,<sup>2</sup> working in the Fatigue Laboratory at Harvard, has shown that such work produces a mean heart rate of 170 in 6-year-old boys, as contrasted with 134 in men of 42 (Table I).

TABLE I  
HEART RATES DURING GRADE WALKING

(The speed was 5.6 km. per hour, and the grade, 8.6 per cent. This raises the oxygen consumption to about seven times basal.)

| AGE (YEARS) | HEART RATE |
|-------------|------------|
| 6           | 170        |
| 10          | 164        |
| 14          | 160        |
| 18          | 150        |
| 22          | 146        |
| 26          | 143        |
| 30          | 140        |
| 34          | 137        |
| 38          | 134        |
| 42          | 134        |

Young dogs have high heart rates; these appear to reflect great sympathetic stimulation. It has been shown by Brouha and his associates<sup>3</sup> that, after the dog has been sympathetomized, his performance during moderate exercise may remain unaffected, in so far as fatigue, accumulation of lactic acid, and mobilization of energy reserves are concerned, and yet a given task will be accomplished with a much slower heart rate, and, therefore, with a much larger oxygen pulse. It appears that before the operation the heart rate is unnecessarily high. These facts suggest that the high heart rates among boys reflect the prodigality of youth as contrasted with the conservatism of age; it is well established that youth excels in bursts of intense activity, but that the older man may be superior in sustained activity of more modest intensity.

Measurements of oxygen consumption during moderate activity show no great variation in over-all mechanical efficiency with age, but, since the heart rate is slower in the older man, it follows that his "oxygen pulse," or the oxygen delivered per beat, is greater than in the young man. The measurements of cardiac output during moderate work do

not show any striking variation between the ages of 20 and 50. Data on this subject are inadequate and need amplification. All of these facts indicate that, although the mechanical efficiency of the body as a whole does not vary much with age, cardiac efficiency may be greater in the older man provided he is in good health. It should be emphasized that we have been discussing efficiency in the true engineering sense, i.e., the ratio of output of useful energy to total energy input. We shall now direct our attention to the *capacity for work*.

The capacity for work of the body as a whole may be measured in a variety of ways. An index to the capacity for anaerobic work is gained by timing a man in a quarter-mile race. An index to his capacity for aerobic work is given by his performance in a marathon race. Corresponding practical tests in military circles would consist in ascertaining how many yards a soldier, carrying his equipment, can cover in one minute, and how many miles per day he can march. Other practical tests are given daily in the wheat field, in the lumber camp, in the steel mill, on the battleship, and in the tank.

TABLE II

MAXIMAL ATTAINABLE OXYGEN INTAKE OF THE AUTHOR FROM THE AGES OF 37 TO 50

| YEAR | MAXIMAL OXYGEN INTAKE<br>(L. PER MIN.) |
|------|--|
| 1928 | 3.28                                   |
| 1930 | 3.26                                   |
| 1931 | 3.35                                   |
| 1933 | 3.23                                   |
| 1935 | 3.26                                   |
| 1936 | 3.17                                   |
| 1937 | 2.90                                   |
| 1939 | 2.98                                   |
| 1941 | 2.87                                   |

Quantitative measurements can be made in the laboratory. They reveal that man's best performance during intense activity is attained between the ages of 18 and 25. His maximum heart rate then lies between 190 and 210, and he can reach higher levels of oxygen consumption during this time than ever again. Thereafter, his decline can be traced. He may be able to use 4 liters of oxygen per minute at the age of 20, and only 3 liters per minute at the age of 50. At the same time, the maximum heart rate he can attain during exercise falls off; it is likely to lie between 160 and 170 at the age of 50, and may not exceed 150 at the age of 70. These observations were made by Robinson,<sup>2</sup> chiefly on a group of nearly 100 men and boys, all of whom were in good health. Although most of these subjects were studied only once, the results are in harmony with observations made on some of ourselves during the past 10 to 15 years. In my own case, for example, my maximum heart rate has declined from about 172 to 162 per minute, and my maximum oxygen consumption from about 3.3 to 2.9 liters per minute, since 1928, as shown in Table II.

Unfortunately, we have no reliable method of measuring cardiac output during maximal activity. There can be no question that, as the capacity for oxygen supply falls off, the capacity for pumping blood declines also, but we do not know how closely this decline parallels the decline in oxygen consumption. The best evidence indicates that it is the young man who is able to utilize the most oxygen as blood passes through the capillaries. He accumulates the highest concentrations of lactic acid in his blood, as shown by Robinson and Harmon;<sup>4</sup> the greater acidity thus produced favors the unloading of oxygen in his tissues. The well-trained young man can accumulate twice as much lactic acid as the untrained man and is able to transform more energy anaerobically on this account.

During the summer of 1939, ten of us from the Fatigue Laboratory set up a temporary laboratory in the high school at Benoit, Mississippi, in order to study the work capacity of young sharecroppers, both white and colored, and to ascertain the effects on our own party of this hot, humid climate.<sup>5</sup> Particular attention was paid to cardiovascular functions. Attempts were made to carry on for two hours enough work to increase the basal oxygen consumption sevenfold. The handicap imposed by temperatures of 85° to 90° F. and a humidity of 80 per cent soon became evident. Sweating began, and soon reached a rate of 1 to 2 liters per hour. Body fluids were thus depleted, and, at a time when the blood volume was decreasing, there was an increased opening of peripheral vessels. The body temperature of the less fit persons (including most of the Northerners) was rising steadily, and their efficiency was steadily becoming less. At the same time the pulse rate was increasing; the cardiac output was declining; and the systolic blood pressure was falling. Some members of our party were unable to continue for more than an hour, and the best of us were nearly exhausted after two hours.

All of the sharecroppers were able to complete the two hours. The white sharecroppers gave a much better performance than our group. They were more fit, and they had the great advantage of being leaner. The negro sharecroppers were much superior to the white sharecroppers. Most of them reached a state of equilibrium with a rectal temperature of about 101° F. and a pulse rate of 150, as compared with 102° F. and 170, respectively, for the whites. They sweated less and drank more, and they had a higher over-all efficiency. We do not fully understand this superiority of the colored men, but believe it depends on a number of factors, rather than on a single factor. Their high efficiency, their lack of surplus fat, and their excellent physical condition contributed to their success in carrying out this severe test, but it is a fair assumption that the superiority of their cardiovascular function was a major factor.

It goes without saying that the two groups of sharecroppers overlapped in their rating on this test. Of twenty-three negroes, two or three

were below the average performance of the whites. Of the seven whites, one was better than the average negro. One of the poorest performances was given by a negro house servant who was later found to have active and untreated syphilis. Additional details are shown in Table III.

TABLE III

WORK PERFORMANCE OF COLORED AND OF WHITE SHARECROPPERS AT A TEMPERATURE OF ABOUT 30° C. AND A RELATIVE HUMIDITY OF 80 PER CENT

|                                 | COLORED<br>SHARECROPPERS | WHITE<br>SHARECROPPERS |
|---------------------------------|--------------------------|------------------------|
| Number                          | 20                       | 7                      |
| Duration of work (min.)         | 120                      | 120                    |
| Final rectal temperature (° C.) | 38.26                    | 38.64                  |
| Final skin temperature (° C.)   | 33.95                    | 34.49                  |
| Final mechanical efficiency (%) | 25.6                     | 27.5                   |
| Final blood lactate (mg. %)     | 27.0                     | 22.3                   |
| Final blood sugar (mg. %)       | 104                      | 114                    |
| Final R. Q.                     | 0.86                     | 0.85                   |
| Final heart rate                | 152                      | 173                    |

These studies support the opinion often expressed by plantation owners that negroes are more resistant than whites to the ill effects of humid heat. It is commonly said that negroes can outwork their mules in plowing cotton. Although it is admitted that our observations are too few to be of great significance, it appears that a comparison of the performance of white and colored troops in the wet tropics might well be carried out in order to test adequately the military importance of these studies.

The same subjects were also tested in a run to exhaustion which lasted not more than five minutes. High temperatures and high humidity may aid, rather than hinder, performance in a test of such short duration. Our principal aim was to compare the performance of sharecroppers with that of northern college students. The former did as well, if not better, in most respects. They attained as high a heart rate; they ran about as long; and their maximal oxygen intake, per unit of body weight, was nearly the same. Of the two groups of sharecroppers, the negroes were somewhat superior to the whites. It may be concluded from these observations that, in such a rich farming country as the Mississippi Delta, conditions permit the development of high physical fitness. We must bear in mind, however, that the high infant mortality among negroes may eliminate the less fit, and that those who were examined were probably more highly selected than the college students, in so far as native physical endowment is concerned.

The heart rate attained during submaximal exercise is remarkably uniform for a given person under given environmental conditions. Some years ago Professor L. J. Henderson prepared two families of curves representing my heart rate and that of Frank Consolazio, my assistant. The external temperature was kept constant in a given experiment, and the heart rate was recorded after ten minutes of graded work on the

bicycle ergometer. The temperature varied from 0° to 50° C., and the oxygen requirement, from 0.6 to 2.6 liters per minute. The humidity at the higher temperatures was kept at about 50 per cent, and the air movement was minimal. The families of curves shown in Figs. 1 and 2 were extraordinarily reliable; the probable error within the range shown was not greater than two or three beats per minute.

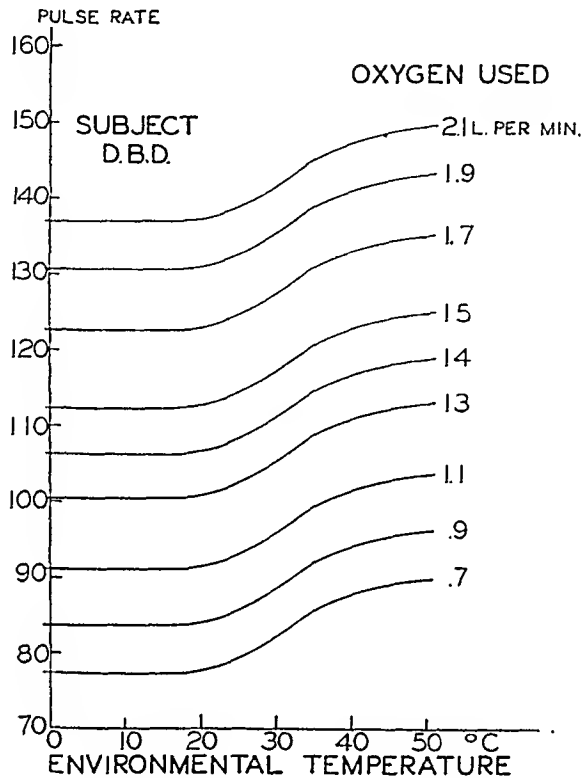


Fig. 1.—Pulse rate of the author as a function of external temperature and grade of work. In the higher temperatures the humidity was about 50 per cent and air movement was minimal. The pulse rate was observed in every instance after ten minutes of work. The mean deviation of the pulse rates from the curves did not exceed two or three beats per minute.

We have been considering, until now, cardiovascular responses to exercise and to the added complication of high temperatures. Turning to another environment, high altitudes, stresses of another sort are presented, namely, inadequacy of oxygen supply with, not infrequently, the hazard of cold. For the aviator there are many additional hazards, of which only one will be mentioned here, i.e., aeroembolism. To simplify the discussion, attention will be directed first to the man who is fully or partially acclimatized to high altitudes, and then to the aviator who has had no opportunity for acclimatization and only a short time for adaptation.

The most extraordinary high altitude communities are on the sides of volcanoes in northern Chile. About 100 men, with some women and children, live on Mt. Ancanquileha at 17,500 ft. Each morning the men climb up a zigzag trail to the mine, at 18,500 to 18,800 ft. There

they spend the day mining sulphur with pick and shovel, and loading it into the buckets of an aerial cable-way. When the day's work is over, they return to camp, where they eat, sleep, and play. Each of these communities has its soccer team, and these were often seen in practice, looking ahead to a Sunday's game at Ollagüe, a mile lower.

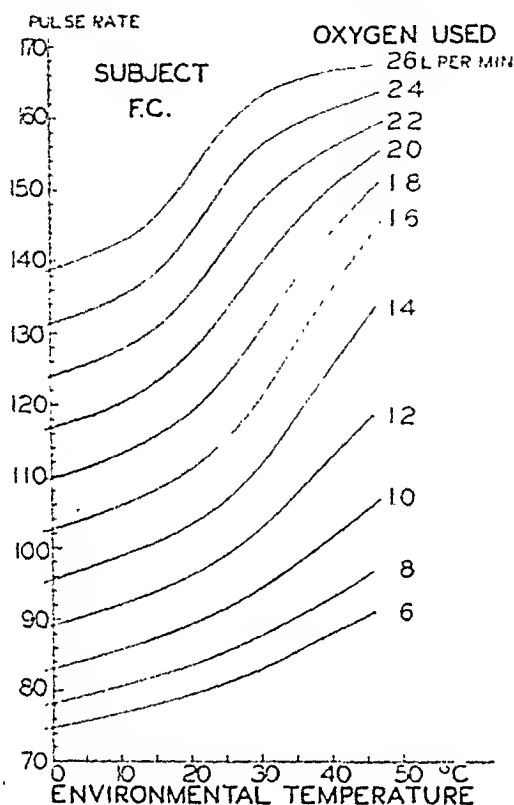


Fig. 2.—Pulse rate of subject F. C.

Our studies of ourselves at altitudes ranging up to 20,000 ft., and of Aneanquileha workmen,<sup>6</sup> revealed the mechanisms of acclimatization which enable man not only to survive, but to carry on a fairly comfortable life at such an altitude. The resting heart rates of the men at Aneanquileha were low—usually between 55 and 70. Their blood pressure was within the usual limits. The most striking change was in the physicochemical properties of the blood. The alkaline reserve was reduced by more than a third, and the hemoglobin was increased 50 per cent. Associated with this increase in hemoglobin there were corresponding increases in erythrocyte counts and hematocrit readings. The blood was so thick that it was difficult to draw it through a 20 gauge needle.

What do these changes imply with regard to the supply of oxygen and the work of the heart? The arterial blood was found to be about 75 per cent saturated. It contained, therefore,  $0.75 \times 30$ , or about 22.5 volumes per cent of oxygen, which is approximately one-sixth more than



is contained in the blood of a normal man at sea level. For rest and exercise, which cause a doubling of oxygen utilization, the calculated oxygen tensions are shown in Table IV. These values are in part hypothetical, but are probably not far wrong. They indicate that the partial pressure of oxygen in venous blood, and hence in tissues, can be kept remarkably high after man has become acclimatized to this altitude. This is possible because of the high level of hemoglobin available for oxygen transport.

TABLE IV  
OXYGEN TRANSPORT AT SEA LEVEL AND AT HIGH ALTITUDES

|  | OXYGEN UTILIZATION<br>(C.C. PER LITER) | ARTERIAL PO <sub>2</sub><br>(MM. HG) | VENOUS PO <sub>2</sub><br>(MM. HG) |
|--|--|--------------------------------------|------------------------------------|
| <i>A. Normal Man at Sea Level</i>        |  |                                      |                                    |
| Rest                                     | 60                                     | 88                                   | 37                                 |
| Work                                     | 120                                    | 88                                   | 22                                 |
| <i>B. Acclimatized Man at 17,500 Ft.</i> |  |                                      |                                    |
| Rest                                     | 60                                     | 42                                   | 30                                 |
| Work                                     | 120                                    | 42                                   | 22                                 |

The dusky appearance of these men was somewhat like that seen in polycythemia vera; it depends on congestion of capillaries with thickened blood. The circulatory handicap caused by the increased proportion of erythrocytes is considerable, but is not as great as might at first appear. The work of Fåhræus and Lindquist<sup>7</sup> indicates that in vessels of the size of arterioles the blood flows in a nonturbulent fashion, i.e., the cells move in an axial stream without much contact with one another or with the vessel walls. The resistance is chiefly caused by contact of the arteriolar walls with the more slowly moving plasma. Since the plasma of the acclimatized man is no more viscous than that of a man at sea level, it follows that the work done in circulating the blood is not greatly increased because of an increased proportion of erythrocytes.

None of our own party attained as complete acclimatization as the residents. Our hemoglobin increased only 25 per cent, and, although we spent from one to three weeks at 17,500 ft., we never became comfortable there. Our work capacity was greatly reduced. The most surprising observation was that the maximum heart rate that could be attained with exercise was less the greater the altitude. Neither could much of an oxygen debt be accumulated. The increase in blood lactic acid after strenuous exercise was less than half normal at 17,500 ft. One day Edwards and I climbed to 20,000 ft., finishing with a final burst of speed, relatively speaking. We at once drew blood from one another; subsequent analyses showed that the lactic acid content was hardly above the usual rest level. Another phenomenon, which is familiar to all climbers in high altitudes, is worth emphasizing, namely, shortness of breath on exertion. This shortness of breath makes climbing a very slow and

usually an intermittent process. One takes a few steps upward and stops to rest. One minute's rest is enough, and this makes it clear, considered in conjunction with the small increases in lactic acid, that the controlling factor is gas exchange, not accumulated, unoxidized end products.



Fig. 3.—Arterial oxygen saturation before and during four minutes of work at 40,000 ft. The subject breathed pure oxygen and attained an oxygen consumption of about 1.5 liters per minute.

Recent studies in the pressure chamber at Wright Field threw light on this phenomenon. With rest or easy work, the conditions shown in Table IV obtained; the arterial  $pO_2$  can be kept up by increased pulmonary ventilation. With such heavy work as climbing, however, the arterial  $pO_2$  drops, the increased anoxia stimulates respiration to a hyperpneic level, and, even so, the oxygen content of arterial blood falls off. Fig. 3 illustrates the fall in arterial  $pO_2$  when hard work is attempted at 40,000 ft., breathing pure oxygen, and the rapidity of recovery. The phenomenon depends on overtaxing of the diffusion capacity of the lungs; although a gradient of 1 or 2 mm. Hg is enough to supply the resting oxygen requirement, this proves wholly inadequate for heavy work.

An additional point of undoubted importance is the effect of the more alkaline state of the blood (produced by hyperventilation, unaccompanied by much lactic acid formation) on the unloading of oxygen. Although this favors the uptake of oxygen in the lungs, it hinders the release of oxygen in the tissues.

This picture, it seems to me, resembles that which is seen in the old man with a healthy cardiovascular system, but with the limitations to which all persons of advanced years are subject. He, too, has a low maximal heart rate; he is unable to accumulate much lactic acid during exercise; he has a reduced capacity for supplying oxygen to his tissues; and he experiences shortness of breath on exertion.

We come now to the stress and strain experienced by the aviator, in so far as they concern his heart and circulation. No acclimatization can be expected in his case because he spends, at most, only a few hours daily at high altitudes. His adaptive responses must be immediate; they are respiratory and circulatory.

Recent measurements of Asmussen and Chiodi, et al.,<sup>8,9</sup> throw new light on the mechanisms of immediate respiratory and circulatory responses to acute oxygen lack. Their work amounts to an extension to intact man of the hypotheses advanced by Heymans<sup>10</sup> and Schmidt<sup>11</sup> and their associates regarding the role of the carotid body in respiratory and circulatory regulation.

Asmussen and Chiodi produced oxygen lack in some instances by moderate carbon monoxide poisoning, and, in others, by means of an air-nitrogen mixture. In each case there was a reduction of 20 to 30 per cent in the oxyhemoglobin of the arterial blood. Physicochemically, the effects on the blood are quite different. The dissociation curve of the available hemoglobin is displaced to the left by carbon monoxide poisoning. In this state the oxygen saturation of the available hemoglobin and the arterial  $pO_2$  will be normal, but, for a given oxygen utilization, the venous  $pO_2$  will be greatly reduced. In the low oxygen experiments—hypoxie hypoxemia—the oxygen dissociation curve is unchanged. The oxygen saturation of the available hemoglobin and the  $pO_2$  of arterial blood will be reduced. If the oxygen utilization is unchanged, the venous  $pO_2$  will be reduced; but to a less extent than in carbon monoxide hypoxemia.

The physiologic effects of these two forms of hypoxemia on the circulation and respiration were measured during rest and two grades of exercise. In summary, the results are shown in Table V.

The respiratory measurements show little increase in the volume of air breathed in carbon monoxide poisoning until work becomes heavy, but very considerable effects when a low oxygen mixture is breathed. It is presumed that in the former state there is no oxygen lack in the carotid body, whereas in the latter state there is a considerable oxygen lack there. This explanation can be maintained if we assume that the oxygen consumption of the carotid body is low in relation to the arterial supply, which we know is abundant, so that the reductions in combined oxygen, and hence in  $pO_2$ , are small. This means that in carbon monoxide poisoning the  $pO_2$  in the carotid body is not much below its usual value. When the  $pO_2$  of the arterial blood which is supplied to the

carotid body is low—as at high altitudes, or when a low oxygen mixture is breathed—the  $pO_2$  within the carotid body will be even lower, and a strong stimulus is transmitted to the respiratory center. An early result of this hyperventilation is to produce an alkalosis which would normally inhibit respiration. A balance must be struck between their opposing forces; evidence of this conflict is seen in Cheyne-Stokes breathing.

TABLE V  
A COMPARISON OF TWO FORMS OF HYPOXEMIA

|  | REST | LIGHT WORK | HEAVY WORK |
|--|------|------------|------------|
| <i>Relative Respiratory Volumes</i>          |      |            |            |
| Normal                                       | 100  | 450        | 750        |
| CO-hypoxemia                                 | 100  | 440        | 950        |
| Anoxic hypoxemia                             | 160  | 650        | 1,360      |
| <i>Average Pulse Rates</i>                   |      |            |            |
| Normal                                       | 59   | 102        | 135        |
| CO-hypoxemia                                 | 67   | 137        | 173        |
| Anoxic hypoxemia                             | 74   | 141        | 172        |
| <i>Average Cardiac Outputs (l. Per Min.)</i> |      |            |            |
| Normal                                       | 4.7  | 11.4       | 15.5       |
| CO-hypoxemia                                 | 5.1  | 12.8       | 16.4       |
| Anoxic hypoxemia                             | 8.8  | 18.7       | 24.1       |
| <i>Average Stroke Volumes (c.c.)</i>         |      |            |            |
| Normal                                       | 80   | 112        | 117        |
| CO-hypoxemia                                 | 76   | 104        | 105        |
| Anoxic hypoxemia                             | 118  | 136        | 143        |

The circulatory responses are somewhat more complicated than the respiratory, for we observe increased pulse rates with an unchanged cardiac output in carbon monoxide poisoning, whereas both are increased in hypoxic hypoxemia. The increased pulse rate in carbon monoxide poisoning may be looked upon as a pressoregulatory compensation for the vasodilation. A stimulation of the circulatory center, in an attempt to compensate for the low  $pO_2$  in the tissues, apparently does not take place. Asmussen and Chiodi conclude from their experiments that acute oxygen lack in tissues is neither directly nor indirectly a stimulus for the circulatory center.

On the other hand, it is obvious that in hypoxic hypoxemia, in which the arterial  $pO_2$  is low, there is stimulation of the mechanisms which regulate the circulation. In this connection, Schmidt and Comroe<sup>11</sup> have shown that a low arterial  $pO_2$  increases pulse rate and blood pressure if the chemoreceptors of the carotid body are intact, but not if they are denervated. It seems reasonable to conclude that the chemoreceptors of the carotid and aortic bodies originate the stimuli that result in the increased cardiac output when the arterial  $pO_2$  is low.

The aviator of today, unless he is foolhardy, does not venture above 15,000 ft. without his oxygen supply, and he does not remain long above

12,000 ft. without oxygen. If he ventures as high as 20,000 ft. without oxygen, he is in danger of collapse. Let us assume, therefore, that he is a pilot in the Army Air Corps, and is provided with the most recent type of oxygen equipment. Our equipment, which was developed by Dr. Boothby, Dr. Lovelace, and Dr. Bulbulian, at the Mayo Clinic, in cooperation with experts in the Materiel Division of the Army Air Corps, is recognized as having limitations, but it has proved both economical and practical in most situations so far faced by Army pilots. With this equipment the pilot can climb to 30,000 ft. without serious oxygen lack. At 40,000 ft. the atmospheric pressure is one-fifth normal, and, even if he is supplied with pure oxygen, the blood does not take up its full quota. The reason for this is simple; the partial pressures of water vapor and of carbon dioxide in the lungs are about the same as at sea level. At sea level their effect is to displace air, but at 40,000 ft. they displace oxygen. Their diluting effect is about five times as great when one is breathing oxygen at 40,000 ft. as when breathing air at sea level. This is illustrated in Table VI.

TABLE VI  
THE DILUTING EFFECTS OF WATER VAPOR AND CARBON DIOXIDE

|                              | BREATHING AIR<br>AT SEA LEVEL | BREATHING PURE OXYGEN |               |
|------------------------------|-------------------------------|-----------------------|---------------|
|                              |                               | AT 30,000 FT.         | AT 40,000 FT. |
| Total pressure (mm. Hg)      | 760                           | 225                   | 142           |
| Alveolar $p_{H_2O}$ (mm. Hg) | 47                            | 47                    | 47            |
| Alveolar $p_{CO_2}$ (mm. Hg) | 40                            | 40                    | 38            |
| Alveolar $p_{O_2}$ (mm. Hg)  | 100                           | 138                   | 57            |
| Alveolar $p_{N_2}$ (mm. Hg)  | 573                           | 0                     | 0             |

There are hazards other than oxygen lack to contend with, not the least important of which is cold. Major Armstrong has discussed, in his book on aviation medicine,<sup>12</sup> the handicap imposed by cold. He estimates that, at a cockpit temperature of 0°F., there is a 30 per cent loss in efficiency in performing necessary tasks, and that the loss may reach 80 or 90 per cent at -30° to -40° F. This ineffectiveness is caused by frosted goggles and windshield, cold hands and feet, and the clumsiness associated with wearing bulky clothing.

There is some interdependence of the effects of cold and of anoxia. Inadequate oxygenation of the blood results in a lowered oxygen tension and dilatation of capillaries in active tissues. The increased capillary bed leads to a diversion of blood from less active areas. This slower movement of blood through the extremities contributes to their chilling. Hence an adequate oxygen supply is particularly important if the cockpit is ineffectively heated.

Although pilots are not likely to experience frostbites, members of the crew are commonly exposed to lower temperatures, both of the air in their compartments and of the metal around them. If the oxygen supply

fails and its user faints, his hands and face may come in contact with cold metal so that serious frostbites may result. In caring for such a man, other members of the crew should remember the hazards of cold as well as the hazard of anoxia. Such a man should continue to receive pure oxygen for some time after returning to the ground. The extra oxygen thus supplied favors recovery of injured tissues.

Aeroembolism has been discussed at some length by Armstrong.<sup>12</sup> It may be experienced at 30,000 ft., and is very likely to occur after some time at 40,000 ft. It takes various forms but always may be attributed to the formation of gas bubbles in tissues or body fluids. The formation of these bubbles has a simple physical explanation--a sudden reduction in pressure to one-fifth atmospheric produces a supersaturated solution of nitrogen; four-fifths of this nitrogen is in an unstable state. Much of it is eliminated by the lungs, but some bubbles form in the tissues. Once a bubble forms it may grow by accretion. Both carbon dioxide and oxygen diffuse into it, so that gas collected from emboli may contain no more than 50 per cent nitrogen.

The symptoms that may be caused by aeroembolism are as follows:

1. *Bends*.--Pains in the joints, particularly the knee and ankle. These usually disappear on descent, but, if they have been present for an hour or longer, they may persist in diminished intensity for some hours at ground level.

2. *Itching*.--This is technically known as formication and is a common symptom. It disappears during descent and leaves no after effects.

3. *Second-degree Formication*.--This may be considered an extension of 2. Presumably, gas bubbles form in the skin and first become evident when they begin to press on nerve endings. These bubbles may impede the peripheral circulation enough to produce cyanosed areas, with perhaps some capillary damage, even though the arterial oxygen is undiminished. The itching stage gradually merges into pain, and the distress may become evident through perspiration, paleness, and other classical symptoms of shock. Most of the pain disappears at ground level, but the itching may persist for twenty-four hours, and red splotches on the skin, suggestive of those which are seen during recovery from severe carbon monoxide poisoning, may not disappear until two or three days have passed. This form of aeroembolism, in our experience, is most common in persons with too much subcutaneous fat. Possibly it is more likely to occur in the low-pressure chamber than in an airplane when the external temperature is low. Formication of the milder sort, however, is often experienced by pilots in high altitude flights.

4. *Throat Irritation*.--At first there is pain on taking a deep breath, and later a generalized irritation of the bronchial tree, accompanied by an unproductive cough. If the pain becomes continuous and more severe, dyspnea becomes evident and collapse may ensue unless one

descends rapidly to lower altitudes. Although this manifestation of aeroembolism is not usually the most distressing symptom, it is one of the most common, judging from our experiences during prolonged exposures to altitudes of 30,000 ft. and above. If the pains have been severe and prolonged, they may persist for some hours after descent.

5. *Headache*.—One of our subjects, after two hours at 30,000 ft., almost invariably develops a mild headache that does not disappear until several hours afterward. We have no proof as to the mechanism, but it may depend on bubbles in the cerebrospinal fluid.

Aeroembolism may be considered one of the most serious problems of the era of military aviation which we are now entering. The most serious aspect of aeroembolism is the prospect of circulatory collapse if the cumulative effects become intolerable. Unfortunately, there is at hand no wholly satisfactory remedy. Much can be done in the way of selecting resistant persons. The preliminary breathing of oxygen while exercising greatly increases one's tolerance, but this cannot be done practically in many situations.

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## THE NORMAL HEART

### ANATOMY AND PHYSIOLOGY OF THE STRUCTURAL UNITS

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SIR ARTHUR KEITH,<sup>1</sup> in a Harveian lecture, quotes Harvey to the effect that "no physiological theory can be true unless it gives a complete and final explanation of all points of structure," and then inquires, "How far does our knowledge of the function of the mammalian heart fall short of explaining its structure?" That cardiac structure has been recurrently interesting and difficult to understand is attested by the following list of fifty-eight investigators, many of them prominent anatomists, who, during five centuries, have studied its morphology and have demonstrated repeatedly that the ventricles are made up of discrete muscle bands:

*In the Sixteenth and Seventeenth Centuries.*—Vesalius, 1514-1564; Stenson, 1630; Seger, 1661; Lower, 1669; Langelotte, 1675; Pecchlinus, 1676; Bartholin, 1678; Borelli, 1681; Charleton, 1683; Morton, 1683.

*In the Eighteenth Century.*—Vienssens, 1706; Winslow, 1711; Keerwolf and Ruy-schius, 1720; Morgagni, 1723; Santorinus, 1724; Lancisi, 1728; Forell, 1732; Stuart, 1738; Walther, 1738-1753; DeBlainville, 1740; Lientaud, 1740; Albinus, 1747; Sennae, 1749; Haller, 1757; Wolff, 1780.

*In the Nineteenth Century.*—Wilson, 1859; Lasehka, 1860; Lindes, 1865; Winckler, 1865; Sappey, 1869; Henle, 1876; Cruveilhier, 1877; Hesse, 1880; Allen, 1884; His, Sr., 1885-1886; Albrecht, 1887; Brown, 1888; MacAllister, 1889; Krehl, 1891; Haycraft, 1891; His, Jr., 1891; Thane, 1894; Kent, 1894; Seipp, 1895.

*In the Twentieth Century.*—MacCallum, 1900; Testut, 1901; Foster, 1901; Toldt, 1901; Knower, 1908; Luciani, 1911; Mall, 1911; Tandler, 1913; Shaner, 1924; Flett, 1927-1928; Robb and Robb, 1934-1941; Lowe, 1939-1941.

There is good agreement among all authors regarding the superficial muscles. Fig. 1, taken from 'Todaro,'<sup>2</sup> shows the fibrous structures at the base of the heart from which the muscles take origin and upon which they again insert. The outer fibers, which arise from the conus tendon, the pulmonary root, the left trigonum fibrosum, and the anterior, lateral, and posterior curvature of the left auriculoventricular ring, were named superficial bulbospiral (SBS) by Mall,<sup>3</sup> in reference to the aortic bulbar (left) side of the heart. There is some variability in the extent of this origin; sometimes the fibers do not reach as far anteriorly and to the right as the conus tendon; sometimes they spread

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backward only to the midportion of the left posterior curve of the mitral orifice; or they may extend further over to the medial curvature of the posterior edge of the tricuspid orifice.

In contrast to the SBS, the outer fibers which arise around the tricuspid orifice were named superficial sinospiral (SSS) by Mall, in reference to the venous or right side of the heart. These two muscles extend spirally downward toward the apex; the superficial bulbo-spiral covers a considerable portion of the diaphragmatic surface of the heart, and the superficial sinospiral covers the most basal portion of the right ventricle posteriorly, much of the right ventricle anteriorly, and crosses in a narrower band to form the anterior horn of the left vortex. Together they cover the whole surface of both ventricles with a muscular layer only about 1 mm. thick, except at points around the base of the heart, where, through fenestrations, the deep sinospiral can be seen.

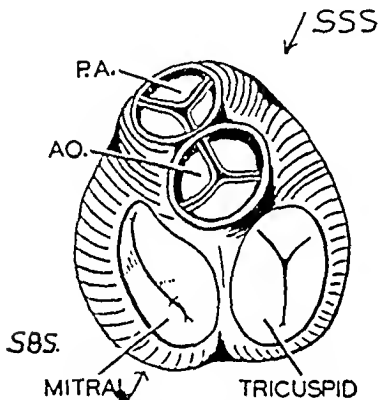


FIG. 439. The four orifices guarded by valves, showing the cusps (also the superficial muscle layer of the ventricle). (After Spalteholz.)

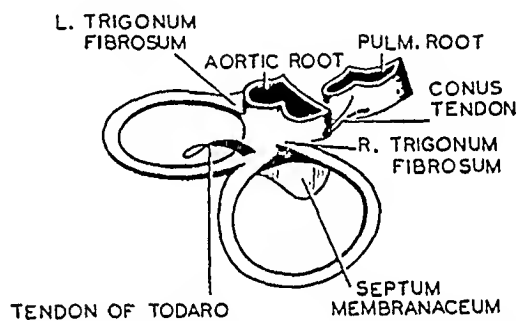


FIG. 440. The skeleton of the heart. (After Todaro.)

Fig. 1.—Copied from Grant: *A Method of Anatomy*, Williams & Wilkins Co., to show, in Fig. 440, the tendinous ring at the base of the heart from which the muscles take origin and to which they again insert. In Fig. 439 the superficial bulbospiral (SBS) arises from the conus (P. A.) and all around the mitral ring toward the left. The superficial sinospiral (SSS) arises around the tricuspid ring.

At the apex of each ventricle, but seen more easily on the left, the fibers form a vortex and penetrate to the interior of the ventricles, where they lie subendocardially and run spirally upward, surrounding both ventricular cavities, to attach to the tendons around the auriculoventricular orifices. This attachment may be either direct or indirect. Some fibers are pulled toward the interior of the ventricular cavities, and so form the papillary muscles, from which fibrous tendons (chordae tendineae) attach to the valve leaflets, and, through them, to the fibrous rings at the base of the heart. The superficial bulbospiral in the right ventricle, as well as in the left, forms a considerable portion of the inferior (posterior) papillary muscle, and attaches through the posterior leaflets of the mitral and tricuspid valves. On the right it

also gives many fibers to the anterior papillary muscle, whereas, on the left, relatively few pass to the anterior papillary muscle. The superficial sinospiral muscle contributes to the anterior and septal papillaries on the right side; it is attached both directly and indirectly, through the anterior and septal tricuspid leaflets, to the fibrous A-V ring. On the left this muscle also attaches directly, or, after forming the anterior papillary muscle, attaches by the chordae tendineae and the anterior mitral leaflet to the corresponding fibrous ring on the left.

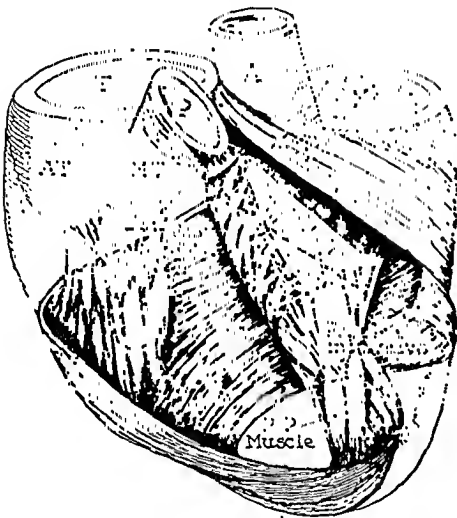


Fig. 2.

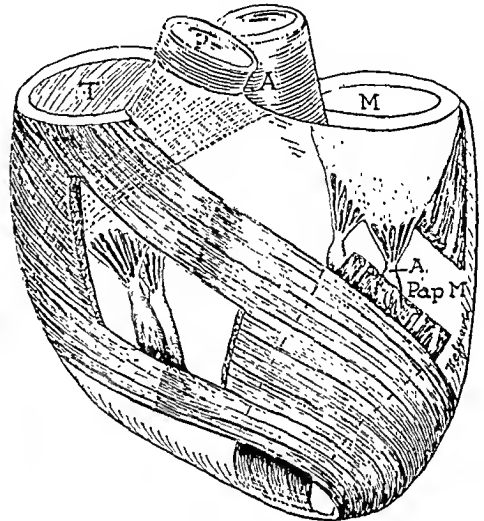


Fig. 3.

Fig. 2.—The superficial bulbospiral muscle as seen from the front of the heart (compare with Fig. 1, Robb, Hiss, and Robb,<sup>2</sup> which is a more schematic diagram of the same muscle, viewed from the diaphragmatic surface of the heart). A, Aorta; M, mitral orifice; P, pulmonary artery; T, tricuspid orifice; AT, anterior leaflet of tricuspid valve; MT, medial leaflet of tricuspid valve; Post. leaf., inferior (posterior) leaflet of the tricuspid valve; P.P. inferior (posterior) leaflet of the mitral valve. A V-shaped section is cut from those fibers encircling the left ventricle subendocardially, so that the mitral valve may be seen. A similar band on the right is not sketched in because of technical difficulties.

Fig. 3.—The superior sinospiral muscle, as seen from the anterior surface of the heart (compare with Fig. 2, Robb, Hiss and Robb<sup>2</sup>). Symbols as in Fig. 2. Again the subendocardial layer has been cut through in order to show deeper structures. The window in the right ventricular wall shows the fibers from the trabeculated area running up to the anterior and medial leaflets of the tricuspid valve. In both of these superficial muscles, blood vessels follow the muscle strands as they encircle the apex, and either surround the ventricles or form the capillaries.

There has been more difficulty regarding definition of the deeper layers, but most authors are in essential agreement, as is shown by a comparison of the drawings by Mall,<sup>3</sup> Tandler,<sup>4</sup> Flett,<sup>5</sup> Shaner,<sup>6</sup> and Robb, et al. (Fig. 4.)<sup>7</sup>

The deep sinospiral muscle (DSS) (called part of the "middle layer" by Shaner,<sup>6</sup> and "Wandfassern" by Tandler<sup>4</sup>) encircles both ventricles, and lies deep to the previously described superficial layers. One portion arises at the anterior curve of the left A-V ring, and its fibers run more transversely than those of the superficial layer; other fibers enter from the whole circumference of this ring. At the posterior interventricular groove, this muscle splits; the deeper fibers enter the septum, whereas those which are less deep (along with those arising from the

right A-V ring) form the lateral wall of the right ventricle. The muscle is deficient toward both apices, for there are large oval apertures which are filled in by the superficial muscles (right and left vortices and papillary muscles) (Fig. 5).

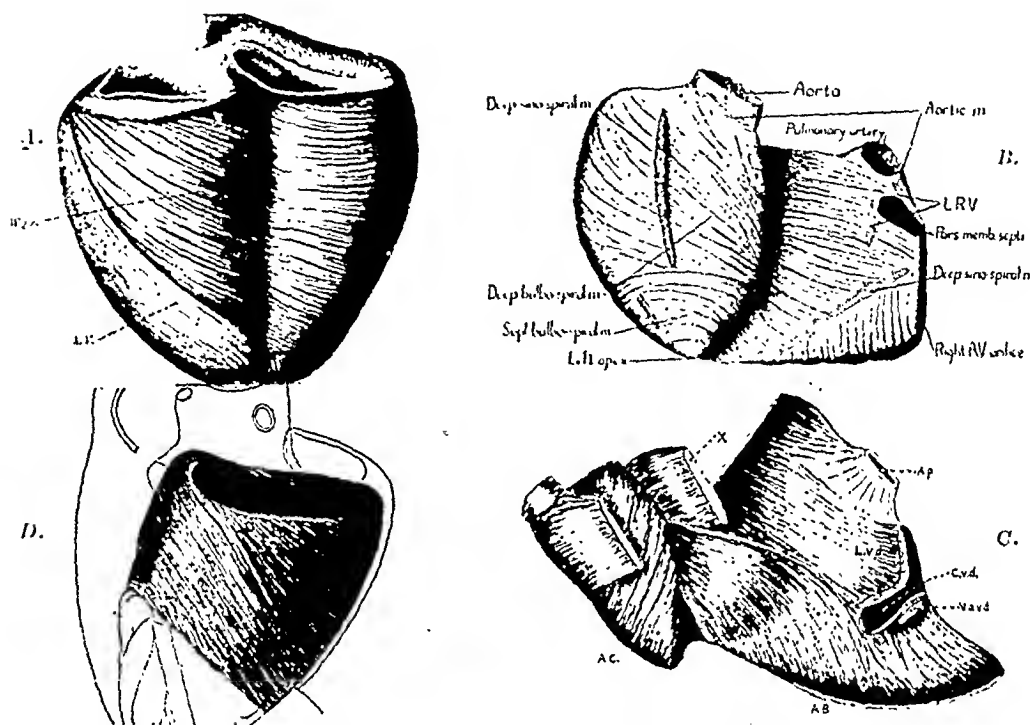


Fig. 4.—A, B, C, the deep sinospiral muscle, as described by three other authors. A, Fig. 51 of Tandler.<sup>1</sup> The dorsal surface of the heart is seen. The superior sinospiral and a little of the superficial bulbospiral muscles have been removed. The nearly transverse fibers of the deep sinospiral muscle are seen crossing the posterior interventricular sulcus. *h.V.*, Posterior "Vortexfasern"; (Mall's superficial bulbospiral muscle); *W.f.r.*, "Wandfasern" of the right ventricle. B, Fig. 6 of Flett,<sup>2</sup> to show the deep sinospiral muscle, also seen from the posterior surface. "Early stage of unrolling of the left ventricle. Aortic muscle and longitudinal muscle of the right ventricle severed." The basal portions of the superficial muscles have been removed. The deep sinospiral muscle has been cut at the posterior interventricular sulcus and the right ventricle pulled laterally. The deep sinospiral muscle fibers forming the medial wall of the right ventricle and part of the septum are well seen. C, Fig. 7 of Shaner<sup>3</sup>; a deep dissection of the fowl heart, posterior view. The deep sinospiral muscle, *AB*, has been cut at the posterior interventricular groove, and the ventricles still further separated. The course of the deep sinospiral muscle through the septum and its attachment on the front of the left ventricle are well seen. *A.B.*, Sinospiral muscle; *A.C.*, superficial bulbospiral muscle; *A.p.*, pulmonary artery; *C.v.d.*, cavity of right ventricle; *V.a.v.d.*, right A-V valve; *X*, deep bulbospiral muscle (cut to show sub-endocardial fibers of superficial bulbospiral muscle). This drawing is almost identical with Shaner's drawing of a like dissection in an adult pig heart, and with Mall's Fig. 8, showing the same structures and relations in a human heart. D, Mall's<sup>4</sup> Fig. 11, an anterior view of the deep bulbospiral muscle. The aorta with the two coronary outlets is seen, as is also the mitral orifice to the left.

The deep bulbospiral (DBS) is the only muscle which is confined to one ventricle. It is a strong circular cuff, and has both its origin and insertion in the medial (septal) curve of the mitral ring. The fibers form three interweaving bands which run circumferentially. This muscle surrounds both the mitral orifice and the aorta (Fig. 6).

The microscopic appearance of the heart is well known, but there is one aspect that deserves consideration. Because syncytial structure is present in the heart, it has been assumed that the whole heart is one syncytium. If this were absolutely true, the results of the labors of

the anatomists who have been cited would have to be considered as artifacts. If one views heart muscle sections which are cut in such a way that some areas are seen in cross section, well-marked septa are found to lie between the various fasciculi. Some of these septa are thicker than others, and, among the connective tissue strands, blood vessels, nerves, and Purkinje-like cells are found. Work is now in progress whereby, with the aid of Dr. Walter Greene, of the Department of Histology of Syracuse University, serial sections are being examined and reconstructions made to ascertain whether the muscle bundles are sheathed throughout their entire course by connective tissue.

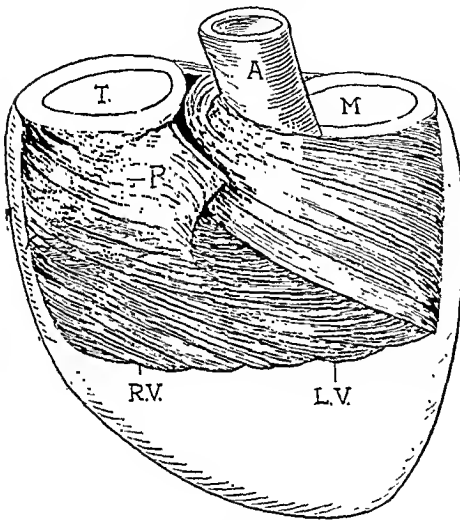


Fig. 5.

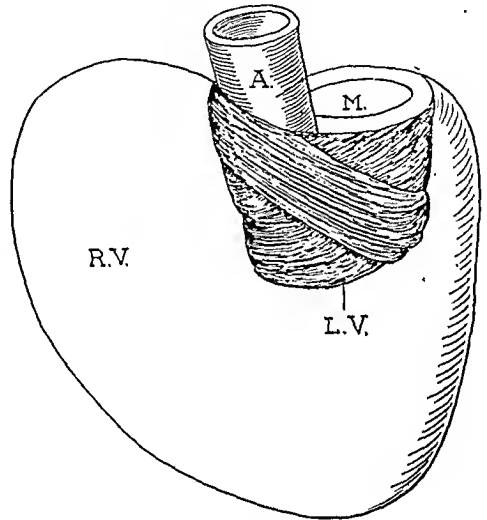


Fig. 6.

Fig. 5.—The deep sinospiral muscle as seen from the front. Note the division of the muscle at the posterior interventricular sulcus, with fibers passing anteriorly to form most of the basal two-thirds of the septum; these septal fibers lie just distal to the band of the left head of origin at the base of the aorta. Symbols as in Fig. 2. (Compare with Fig. 4, Robb, Hiss and Robb,<sup>7</sup> which is the same muscle sketched from the posterior view.)

Fig. 6.—The deep bulbospiral muscle, a powerful sphincter encircling the left ventricular base and enclosing both the aorta and the mitral orifice within its sweep. (Compare with Fig. 3, Robb, Hiss and Robb,<sup>7</sup> which is the same muscle seen from the posterior surface of the heart.)

The anatomists have been chiefly concerned in describing the course and attachments of these muscles, but a few have discussed function. In this laboratory, further study has been made of their (1) blood supply, (2) nerve supply, (3) electrical properties, and (4) function.

1. *Blood Supply*.—An adaptation of a Spalteholz-Banchi diagram indicating which coronary branches are distributed mainly to individual muscles has been published previously.<sup>40</sup> One should note that the coronary branches therein indicated are small. This information was first obtained by gross dissection and was later confirmed experimentally when such branches were tied. After an acute experiment the vessel peripheral to the ligature was injected with a dye, and dissections were made to confirm the localization. Still later, recovery experiments were performed, and the deposition of scar tissue was studied with reference to the muscle involved.

At the apices of the ventricles, where the superficial museles penetrate to form the so-called papillary museles, the more distal branches of the coronary tree (which have been bowed around in a series of arches concave toward the base of the heart) follow the musele; they lie parallel to the musele fibers, and run longitudinally from apex to base. These vessels supply the layer of musele which lies nearest to the endocardium, thus making it unnecessary to postulate either direct nutrition from the ventricular cavity or a nutritive function of the Thebesian system (under normal conditions) to account for the fact that a thin layer of normal tissue lies adjacent to the endocardium when infarction has been produced by occlusion of a vessel which penetrates the thickness of the ventricular wall. This fact may prove to be very important in interpreting abnormal electrocardiograms and localizing lesions.

Our observations may be related to those of Schlesinger<sup>9</sup> that "coronary arteries in normal human hearts, even senile hearts, are true 'Cohnheim end arteries' without anastomotic connections; such anastomoses do not develop *pari passu* with increase in age." A conclusion of Blumgart, et al.,<sup>10</sup> is also pertinent: "In normal hearts intercoronary anastomoses larger than 40 micra in diameter are not found. Anastomotic communications measuring less than approximately 40 micra in diameter exist between the coronary arteries of normal hearts; their presence can be demonstrated by high pressure injections of watery solutions. These fine communications are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion." Karsner and Dwyer<sup>11</sup> had previously shown that coronary arteries are end arteries.

Lowe<sup>12-15</sup> has confirmed these observations by several unique methods. First, he dissected hearts from persons who were known to have had coronary attacks and found that the scar tissue followed musele bundle distribution. Second, he investigated the heart from a patient who died of acute leucemia and found petechiae only along the blood supply to the superficial bulbospiral musele. Third, he examined ruptured hearts and found that the pathway taken by the blood escaping through the wall was partly determined by the connective tissue sheaths between the musele bundles along which dissection by pressure had occurred. Finally, he showed that "a gelatine mass can be injected into the vessels of a single ventricular musele, provided a dynamic balance be maintained between the various branches of the system." Thus, our anatomic and experimental observations on dogs, namely, that coronary arteries are functionally end arteries and are limited in distribution to one musele alone, have been confirmed in man. Lowe concludes: "The evidence that there is a series of separate musele bundles in the ventricular wall of the mammalian heart, and that they function independently, is now very strong."

2. *Nerve Supply*.—The nerve supply of the mammalian ventricle has not been too well worked out by histologists. Sympathetic and parasympathetic fibers are distributed to the auricles and to the coronary arteries, but, to our knowledge, have not been traced to ventricular muscle. Glomset and Glomset<sup>16</sup> report that, in sheep, cattle, and hogs, large numbers of nerve strands enter the main bundle of His, form a conspicuous portion of its cross-section area, and also accompany smaller strands. They also write that "such nerve elements are found neither in the bundle nor in its subdivisions in man or dog."

The Purkinje system has been more thoroughly studied in ungulates than in the dog or man. Two main reasons for this are that in cattle the Purkinje cell retains its individuality, and does not mimic the histology of the heart muscle cell; also, in ungulates, this system is surrounded by a connective tissue sheath which can easily be injected with a colored substance; then, by dissection or corrosion, or by clearing methods, the myocardial distribution is readily followed, and can also be checked microscopically. This sheath is not continuous with the lymphatic system of the heart which was recently described by Drinker.<sup>17</sup> In ungulates the Purkinje system consists of a main bundle, right and left branches, a subendocardial network, and a myocardial network. The myocardial network has been described by Wahlin<sup>18</sup> and Abramson and Cardwell,<sup>19, 20</sup> among others. These papers may be consulted for critical analysis and bibliography. Mahaim<sup>21</sup> described a myocardial network along the right branch in the human heart. In the beef heart the main branches have been shown by Robb, Greene, and Robb<sup>22</sup> to be distributed to specific muscle bundles.

There has been a tendency for physiologists and cardiologists to assume that this system is distributed in the human heart in the same manner as in the beef heart. However, although Mahaim,<sup>21</sup> Tawara,<sup>23</sup> Mönckeberg,<sup>24</sup> Lewis,<sup>25</sup> and Yater<sup>26</sup> described an A-V node, Todd<sup>27</sup> and Glomset and Glomset<sup>16</sup> did not find a circumscribed node in the human heart to compare with that found in ungulates. Also, in the human heart, right and left branches were not found by Glomset and Glomset,<sup>16</sup> although they have been thought to be present by many others, especially by Mahaim,<sup>21</sup> Yater,<sup>26</sup> Wahlin,<sup>18</sup> and Oppenheimer, et al.<sup>28, 29</sup> Histologic reports on human heart sections taken from areas where one might expect to find Purkinje tissue do not agree, but range from one extreme, at which true Purkinje or "Purkinje-like" cells are described, to the other, at which these groups of fibers are said to be composed of ordinary myocardium. Possibly this disagreement results from personal equation, for Yater<sup>26</sup> stated that the bundle fibers resemble the ventricular fibers, but possess less myoplasm, and Mahaim<sup>21</sup> stated they can only be identified by following a given strand of tissue in serial sections.

There is also variance regarding the myocardial networks. Todd and van der Stricht,<sup>27</sup> who studied human hearts, found Purkinje cells ex-

tending "to the furthest extent of the ventricular myocardium." Glomset and Glomset<sup>16</sup> report that "cells which correspond to the description of Purkinje cells in man and the dog and to the drawings of these cells by Tawara<sup>23</sup> (Tafel V) are found under the endocardium in various parts of the ventricles. Such cells are often continuous with ordinary myocardial elements." Yater<sup>26</sup> stated: "Purkinje fibers in the substance of the human heart are impossible to recognize but doubtless exist, just as they do in the hearts of large animals." Oppenheimer (personal communication) stated that, although he found "Purkinje-like" cells in the human heart, he had never succeeded in serial sections in tracing the actual transition from these so-called Purkinje cells to ordinary myocardial cells. Todd<sup>27</sup> has stated his belief that all mammalian hearts have an essentially similar Purkinje system, but warned against the belief that no secondary pathways from auricle to ventricle exist (see Kent<sup>30</sup>). Todd<sup>27</sup> vigorously denied that there is an anatomic basis for the current conception of the origin and spread of the action current in the human heart. It is apparently a universal observation that, when Purkinje tissue has been traced to its final distribution, it becomes oriented in a plane parallel to the muscle fibers. This is true, of course, only for the most distally recognizable portion of a given pathway. Thus, in the bovine myocardium, the direction of terminal Purkinje fibers and muscle fibers is identical.

In conclusion, in the beef heart the existence of a bundle of His, right and left branches, a subendocardial Purkinje network, and a myocardial network with specific branches to the separate ventricular muscles is established, but whether a similar system, composed of either Purkinje, Purkinje-like, nerve, or even ordinary cardiac muscle cells, exists in the human heart is still being questioned.

3. *Electrical Effects.*—The discovery that these muscle bands possess specific electrical properties rests on experimental evidence. If one alone of the four muscle bands is injured, either by acute or chronic ischemia, or by undue stretching, or by the application of chemicals, such as potassium chloride, a change in the electrocardiogram always occurs, and this change is always the same for a given muscle.

Can this experimental observation be correlated with the usual concepts of electrocardiograms, and also with the anatomy of the conducting system? The statement that the action current passes along the bundle of His and its branches toward the apex of the ventricles, and thence along the subendocardial network, and arrives eventually at the base of the interior of the ventricles is consistent with our knowledge of ungulate cardiac anatomy. The theory of radial penetration is not consistent with known anatomy. We have shown in the beef heart that, in its final distribution, the Purkinje cell is parallel to the muscle fiber. If there were only radial penetration of the action current in all parts of the heart, there would have to be radial penetration of the conducting tissue, whatever the histologic structure of this conducting tissue. In no heart does

any considerable portion of the Purkinje tissue penetrate radially, and in no heart does ordinary muscle fiber penetrate radially from endocardium to epicardium except at the apex. Even if one were to suppose that the action current passes longitudinally in some muscle fibers and transversely in others, the connective tissue barriers which separate layers with unlike blood supply are still to be considered.

The fact that the electrocardiograms of ungulates possess positive and negative waves which are similar to those of man (and dogs) suggests that the conduction pathways, whatever their histologic structure may prove to be, are similarly arranged in the two orders.

If, in man, it were proved that there is a conducting pathway (special tissue, or ordinary muscle, or even nerves) with a distribution similar to that of the Purkinje system in ungulates, the classical statement that the action current passes along the bundle, its branches, and the subendocardial network would be given anatomic support which it lacks at present. Our experiments have led us to suggest that the action current is distributed to each ventricular muscle individually, and that, where the wall is thin, as at the apices, the trabeculated area, and the pulmonary conus, the pathways are demonstrably shorter. The pathway to the deeper muscles at the base of the ventricles is longer, so that the negativity must be later. The sheaths separating these muscles, which need not be conspicuous to prevent spread of current, may prove to be the critical factor in explaining the electrical changes which are characteristic of a lesion limited to a single muscle band.

4. *Function*.—Harvey<sup>31</sup> and Borelli<sup>32</sup> thought that "the true action of the muscle of the heart is the contraction of the ventricles and the compression and expression of the blood contained in them." Both Pettigrew<sup>33</sup> and Tandler<sup>4</sup> discussed function, but the most detailed suggestions were made by Keith<sup>1</sup> and Flett.<sup>5</sup> Haycraft<sup>34</sup> and Krehl,<sup>35</sup> in the same year, described two fulcrums of the heart—one fixed by mediastinal attachments, and another (apical) which is active by virtue of the fact that the longitudinal fibers of the superficial muscles which run up to the A-V ring do not cause shortening of the septum from apex to base, but, when contracted, fix the apex and prevent its bulging and rupture. Inasmuch as the exterior portions of the superficial muscles are oblique, they do not cause apex to base shortening but do produce a certain rotation of the apex. Flett<sup>5</sup> affirmed this explanation.

Certain facts are well established. The superficial muscles possess an internal portion which constitutes the papillary muscles. Physiologists agree that the time of initial negativity at the interior and exterior of the apices of the two ventricles is early. Recently Rappaport and Sprague<sup>36</sup> reported that heart sounds were present during the period of isometric contraction. These facts give anatomic and physiologic support to the conception that the superficial muscles have two definite functions, namely (1) to fix the apical fulcrum, and (2) to fix the A-V valve leaflets. It would be impossible to have a period of rising tension with



isometric contraction unless the ventricular cavity were closed. In order to close the ventricular cavity, both the semilunar and A-V valves must be in firm apposition. To prevent the A-V valves from bulging into the auricles, thus allowing regurgitation, the valve leaflets must be fixed, and, to accomplish this, the papillary muscles must be contracted in order to keep the chordae tendineae tense. Early contraction of these superficial muscles also seems necessary if one is to explain why the apical area does not normally bulge outward to form an aneurysm, for, in some places, the wall is scarcely 1 mm. thick.

Two clinical observations can be explained if this is the function of these muscle bands. First, a mitral murmur sometimes develops after apical infarction. It is probable that this is due to inadequate tension of the damaged muscle on the valve leaflet, rather than to dilation of the rather heavy fibrous rings at the base of the heart. Second, when an apical aneurysm has developed, and this predicates damage of the two superficial muscles, the thinned apex does bulge during systole. This is also consistent with the observation that, in high-grade mitral stenosis, with calcification, when the left intraventricular pressure is low, the papillary muscles are small, whereas, in conditions such as hypertension and aortic stenosis, in which intraventricular pressure is abnormally increased, the papillary muscles are commonly hypertrophied. The same type of analysis applies to the right side of the heart.

The deep sinospiral muscle forms the main mass of the right ventricle, and must be responsible for maintenance of the pulmonary circulation. When this muscle fails, right-sided heart failure occurs. The left portion of this muscle is also large and, because of the direction of its fibers, can have no other function than expulsion of blood. When this muscle is injured, either in the right or the left portion, a considerable fall of blood pressure takes place.

Hesse,<sup>37</sup> Krehl,<sup>35</sup> and Flett<sup>5</sup> thought that the deep layers take the blood which has been "wrung" out of the lower third of the heart and force it into the aorta. In 1921, Samways<sup>38</sup> and Campbell<sup>39</sup> stated that, structurally, the semilunar valves are not competent to close the aortic orifice against the elastic recoil of the aortic wall, and insisted that some other mechanism must support these valves. The only structure in an anatomic position to do this, according to Flett,<sup>5</sup> is the deep bulbospiral muscle, and he emphasized the probability that it contracts later than the other muscle fibers. If the deep bulbospiral contracted early, it would produce narrowing of the aortic outlet, and this would be equivalent to aortic stenosis. Since it contracts late, it completes the emptying of the ventricle, supports the blood column in the aorta, and, when it relaxes, the aortic valves fall back into position and maintain the diastolic pressure. Presumably, the period of isometric relaxation is that period when the superficial muscles which first went into contraction are recovering, and before the deep sinospiral and (on the left) the deep bulbospiral have relaxed sufficiently to allow differential pressures to

open the A-V valves. According to this explanation, the deep bulbo-spiral recovery phase would end at a variable time after the second sound, i.e., it would vary with the filling of the heart, the tension developed, and the nutrition of the muscle and its mass; this would account for the well-known inconstancy of the relation of the second sound to the end of the T wave of the electrocardiogram.

#### SUMMARY AND CONCLUSIONS

Observations on the structure of the heart made by anatomists during the past five centuries have been reviewed. From these numerous sources certain conclusions are drawn:

1. The mammalian ventricle is composed of several separate muscles.
2. If heart muscle is examined in cross section, connective tissue sheaths are seen between various planes of contractile tissue. Work is now in progress in the hope of ascertaining whether these sheaths extend throughout the course of a given muscle band.
3. Functionally, coronary arteries are end arteries.
4. We have suggested, and Lowe has confirmed, that each ventricular muscle has its own source of blood supply under normal conditions. These conditions may be disturbed if side pressures are lowered by disease processes, for then the small anastomotic channels open. Normally, these channels are present but nonfunctioning.
5. It is known that, in the beef heart, each of the four main ventricular muscles has a direct Purkinje supply, only a small portion of which penetrates radially from the endocardium toward the epicardium. Work is in progress to ascertain whether, by the reconstruction of serial sections of small human hearts, the existence of a distributing system can be demonstrated.
6. Many types of experimental procedures have proved that damage to a given ventricular muscle produces a constant and characteristic change in the electrocardiograms of dogs, monkeys, cats, and rabbits. The full explanation of these changes, which we have also observed in man, and which Lowe has seen, has been difficult to reconcile with the generally accepted theories of electrocardiography which ignore the presence of connective tissue sheaths separating muscle layers with different blood supplies; these sheaths set up a boundary between normal and damaged tissue.
7. Anatomists of note agree that these ventricular muscles have specific functions; the superficial muscles fix the fulcrums so that the septum and the weak-walled apices do not bulge during systole. They also fix the auriculoventricular valve leaflets, and thus prevent regurgitation into the auricles during ventricular systole.
8. The deep sinospiral muscle has an expulsive function and maintains the pulmonary circulation. Its left portion also plays an important part in emptying the left ventricle.

9. The deep bulbospiral muscle provides expulsive force for the left ventricle and is essential in maintaining the aortic pressure toward the end of systole.

10. In experimental animals, survival is possible if both superficial muscles and/or the deep sinospiral are injured. When the deep bulbospiral is damaged the animals never survive.

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# THE SYNDROME OF RUPTURE OF AN AORTIC ANEURYSM INTO THE PULMONARY ARTERY

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A REVIEW of the current textbooks of medicine, physical diagnosis, and cardiology reveals a paucity of accurate data on the clinical course and physical phenomena of a fistulous opening between an aortic aneurysm and the pulmonary artery. Hope<sup>1</sup> studied a patient who was admitted to the Edinburgh Infirmary, Oct. 30, 1833, and subsequently described the clinical features, physical phenomena, and post-mortem observations in a report entitled: "Case of Rupture of a Dilated Aorta Into the Pulmonary Artery." Hope's description of the syndrome is so nearly perfect that it is difficult to understand why it has been practically ignored by subsequent writers.

After Hope's report, the next most comprehensive review is that by Peacock,<sup>2</sup> in 1868. He collected eighteen cases from published reports and added one case of his own. In 1907, Kappis<sup>3</sup> again reviewed the previously reported cases, thirty-two in number, and discussed his personal experience in one case.

A review of the literature since Kappis' publication reveals scattered case reports,<sup>4-9</sup> but no attempt by the authors to define a syndrome comparable to that described by Pepper and Griffith,<sup>10</sup> in 1890, which accompanies the establishment of a fistulous connection between an aortic aneurysm and the vena cava.

The three cases which are here reported were studied by many observers, and, although there was no uniformity of opinion, the symptoms and signs were similar in their essential aspects in all of them. The differences were attributable to variations in the size and location of the aneurysms, the size of the fistulous openings, and the associated cardiovascular disease. In the first case, which was observed in 1929, the correct diagnosis was not made, but it was specifically noted that the physical phenomena and clinical course were not in keeping with the diagnosis of uncomplicated aortic regurgitation and aortic aneurysm. The second patient, who was studied in 1937 and 1938, had a conditional diagnosis of a fistulous opening into the pulmonary artery. In the third case there was an unconditional diagnosis of this complication of aortic aneurysm.

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## CASE REPORTS

CASE 1.—G. Z., aged 55 years, a white, male farmer, was admitted to the Medical College of Virginia Hospital Feb. 23, 1929.

*History.*—He complained of an indefinite pain in the upper and anterior part of the right side of the chest, cough, and breathlessness. Three weeks previously he had been ill from an attack of "influenza." During this illness he suffered pains in his back and limbs; his cough was troublesome; and he had fever for one week. He was confined to bed for two weeks. Three days before he entered the hospital the pain in the right side of the chest became worse, and dyspnea was so severe that he could rest only when he was propped up in bed. Nothing significant was revealed in the past history or family record.

*Physical Examination.*—The patient was a well-nourished and well-developed man in an orthopneic position. There was moderate cyanosis of the lips, mucous membranes and finger tips. His temperature was 98° F.; his pulse rate, 70 to 80 per minute; and his respiratory rate, 22 to 26 per minute. The pupils were equal, and their reaction was normal. The ears, nose, and mouth were normal. The neck veins were markedly distended, even in the orthopneic position. The thorax was barrel-shaped, and hyperresonant to percussion except over the bases, where the percussion note was dull. Medium, moist râles were heard over the bases posteriorly, and the breath sounds were generally suppressed; the physical phenomena indicated emphysema, with mild pulmonary stasis and a moderate effusion in the right pleural cavity. There was a definite increase in supracardiac dullness. The right cardiac border was not definitely located, but the apex beat and point of maximum intensity were in the sixth intercostal space, 12.2 cm. from the midsternal line. Over the base of the heart, in the left second and third intercostal spaces, 1 to 2 cm. from the sternal margin, a distinct systolic and a less distinct diastolic thrill could be felt. Over this same area, with the maximum intensity 2 cm. to the left of the sternal margin in the third intercostal space, a whirring systolic and diastolic murmur was heard. The murmur was "quite similar to that occurring in patients with patent ductus arteriosus." The systolic phase was harsher, louder, and of greater duration than the diastolic. There was a systolic apical murmur, but no diastolic murmur was heard. The second sounds were not significantly altered. The blood pressure was 105/30 in each arm, and 140/35 in the right leg. The pulse was of the Corrigan type. The abdomen was moderately distended, suggesting ascites. The liver was enlarged and tender. There was moderate edema of the ankles.

*Laboratory Examination.*—The blood Wassermann reaction was strongly positive. Examination of the blood showed: Erythrocytes, 5,100,000; hemoglobin, 91 per cent; leucocytes, 8,750; neutrophils, 70 per cent; lymphocytes, 19 per cent; monocytes, 11 per cent. The specific gravity of the urine was 1.022, and there were occasional granular casts. Roentgenographic study: "The patient has a saccular aneurysm the size of an orange extending forward and to the right from the ascending portion of the aorta. The heart is mitral in shape, and moderately enlarged. There is moderate pulmonary congestion, and a small amount of fluid in the right pleural cavity."

*Clinical Diagnoses.*—(1) Aneurysm of the ascending aorta; (2) congestive heart failure, preponderantly of the right ventricle; (3) "The diastolic murmur and vascular phenomena suggest aortic insufficiency, but this diagnosis is not in keeping with the manifestations of right-sided heart failure. Cor pulmonale is suggested by the manifest emphysema and bronchiectasis."

*Course.*—The patient became more cyanotic and breathless, regardless of energetic treatment. He died March 4, 1929.

*Autopsy (partial).*—Only the heart was removed for examination by Dr. L. C. Pusch (Fig. 1).

The specimen consisted of a heart with the entire aorta attached. It was not weighed because of the large amount of aorta and aneurysm attached. The heart appeared only slightly enlarged. The left ventricular wall measured 16 mm. in thickness; the right, 6 to 9 mm. All of the valve rings were competent, and the leaflets were thin, smooth, and pliable. The entire ascending portion and part of the transverse portion of the aortic arch were greatly dilated in a single large saccular aneurysm which measured 12 by 9 by 5 cm. This arose 5 mm. above the commissures of the aortic valve leaflets and extended to the origin of the left subclavian artery. The innominate artery and the left common carotid artery arose from the aneurysmal sac, and the left subclavian arose from the undilated aorta.



Fig. 1.—Case 1. The specimen is viewed from the right, showing the right ventricular enlargement. The pulmonary artery has been opened, exposing the fistula.

Much of the aneurysmal sac was filled with old, laminated thrombus and blood clot. Two and one-half centimeters above the aortic valve commissures, on the left side of the aneurysm, there was a rough, ovoid opening in the wall of the aneurysm which measured 1 by 1.2 cm. This fistula opened into the pulmonary conus at a point 2.5 cm. above the commissures of the pulmonic valve.

CASE 2.—W. R. D., a white man, aged 50 years, was first admitted to the medical service of the Medical College of Virginia Hospital Dec. 26, 1937, and discharged Jan. 23, 1938.

*History.*—The patient had been a reporter for twenty years, but, because of economic difficulties, he had moved to the country in April, 1937. He noticed some breathlessness when he began farm work, but this was attributed to smoking and unaccustomed physical activity. He was definitely restricted in his activities by fatigue and breathlessness, but he continued to work, with moderate limitations. On Dec. 18, 1937, while pitching hay in the barn, he was seized with a constricting sensation over the anterior part of the thorax. This was associated with a pounding in his chest and severe dyspnea. The dyspnea became progressively worse and was continuous, and there was a hacking, nonproductive cough. By December 23 he had become orthopneic. He was uncomfortable in any position, and the dyspnea was so distressing that he was unable to speak or drink fluids in comfort. The past history suggested a syphilitic infection at the age of 22 years, but otherwise was not contributory.

*Physical Examination.*—The patient was a fairly well-developed, undernourished white man, sitting up in bed, with his head resting on a pillow placed on a bed table. The dyspnea was continuous and so severe that talking was difficult, and he avoided the slightest physical effort. The oral temperature was 99.2° F., the pulse rate 98, and the respiratory rate, 28 per minute. There was no visible cyanosis. The eyes, ears, nose, and throat were not remarkable. The cervical veins were markedly distended, and the venous pressure was 240 mm. of water. The lungs were resonant throughout. There were a few medium, moist râles over the lung bases posteriorly, and the breath sounds were distinctly harsh in quality and increased in intensity. There was a moderate increase in the width of the supracardiac dullness. The cardiac apex was seen and felt in the fifth intercostal space, and the left cardiac border was 12.5 cm. to the left of the midsternal line in the fifth intercostal space; the right cardiac border was 5 cm. to the right of the midsternal line in the fourth intercostal space. Over the base of the heart, centering at the left second and third intercostal spaces, 1 to 3 cm. from the sternal margin, a "purring" systolic thrill and a questionable diastolic thrill were felt. Over this same area there were a whirring, intense, systolic murmur and a less distinct diastolic murmur. The diastolic murmur was not constant except when the patient was in the erect position, and it was localized to a small area along the left sternal margin. The systolic murmur was heard over a larger area, even at the angle of the left scapula. There was no Austin Flint murmur. The aortic second sound was slightly amphoric in quality, and of normal intensity, but the pulmonic second sound was markedly increased in intensity. The pulse was rhythmic and typically Corrigan in type. The blood pressure was 140/40-20, and a snapping sound could be heard to the zero point on the manometer. The liver was tender and extended 6 cm. below the costal margin. There was edema of the sacral area and the lower extremities.

*Laboratory Examination.*—The blood Wassermann and Kline reactions were positive. Examination of the blood showed: Erythrocytes, 3,420,000; hemoglobin, 70 per cent; leucocytes, 9,750; neutrophils, 79 per cent; lymphocytes, 17 per cent; and monocytes, 4 per cent. The urine was normal. Roentgenographic study: "The teleroentgenogram showed the heart 18.2 cm. in transverse diameter with a cardio-thoracic ratio of 59 per cent. The aorta in its ascending portion was moderately increased in diameter, but there was no sacculation. The heart was mitral in shape. There was moderate pulmonary stasis" (Fig. 2). Electrocardiographic study showed sinus tachycardia; the rate was 115 per minute (Fig. 3). The kymograph is shown in Fig. 4.



*Clinical Diagnosis.*—Syphilitic aortitis, with aortic insufficiency. "This diagnosis is, however, debatable for the following reasons: (1) The dyspnea is continuous and intense, not paroxysmal; (2) The murmur is at times continuous, and the systolic murmur dominates the auscultatory phenomena; (3) The failure is predominantly right-sided, like that of mitral disease; (4) There is no Austin Flint murmur; (5) The roentgenograms and electrocardiogram are not indicative of aortic valve insufficiency."



Fig. 2.—Case 2. Teleroentgenogram showing a "mitral" configuration, and marked right ventricular enlargement.

*Hospital Course.*—Digitalis was administered in adequate quantities, with only slight improvement. On Dec. 29, 1937, phlebotomy was done; 500 c.c. of blood were removed, but with only moderate relief of the dyspnea. On Jan. 9, 1938, the patient was started on a series of intravenous injections of mercurial diuretics. From this point improvement was rapid, and the patient was discharged on the twenty-eighth hospital day as an ambulatory patient to the cardiac clinic. When he left the hospital, all objective signs of congestive failure had disappeared, but physical activity easily induced breathlessness. He was observed in the outpatient clinic at weekly intervals from Feb. 18, 1938, to April 4, 1938. During this period he continued to take digitalis and restricted his exercise.

*Second Hospital Admission.*—He was readmitted April 5, 1938. During this hospital stay the clinical course was characterized by moderate breathlessness, but

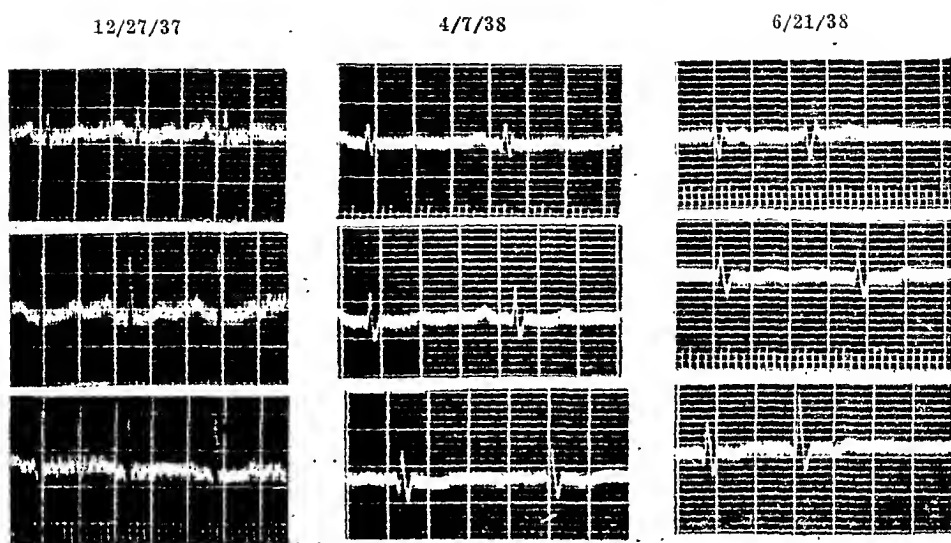


Fig. 3.—Case 2. The electrocardiogram shows transition from a normal axis to a right axis deviation.

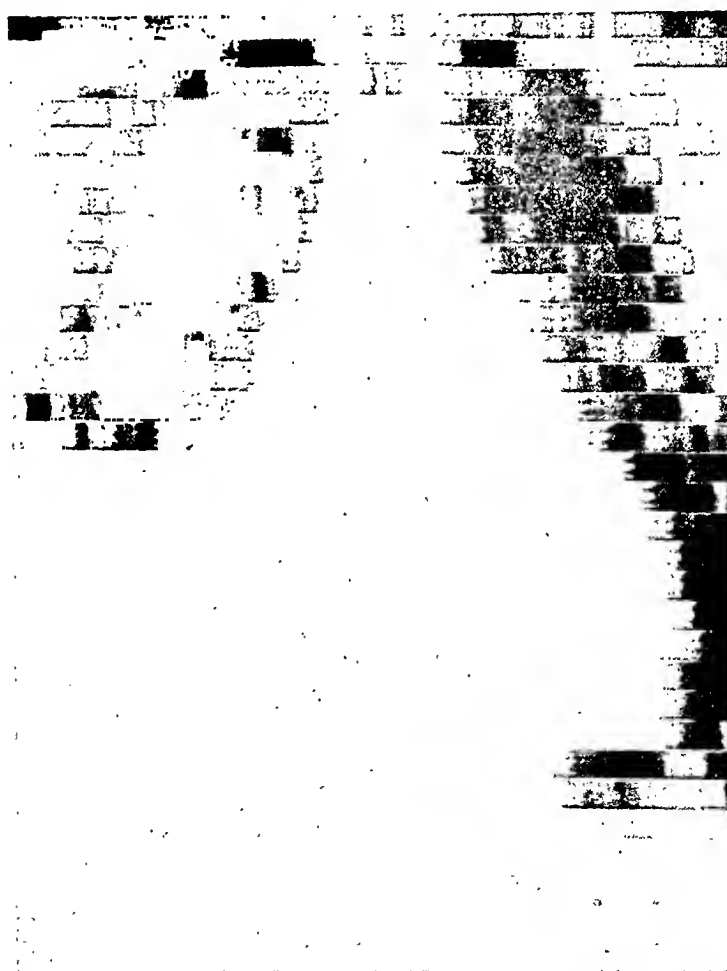


Fig. 4.—Case 2, Kymogram shows wide amplitude of the contraction waves, suggesting aortic insufficiency.

it was never so severe as that suffered during the early period of the first hospital stay. High venous pressure, with hepatic enlargement, edema, and ascites, characterized the clinical picture. The phenomena of pulmonary edema were conspicuous by their absence. Recurring effusion into the right pleural cavity required aspiration, as follows: 1,000 c.c. on July 4; 900 c.c. on June 9; 1,700 c.c. on June 17; and 1,750 c.c. on June 25; making a total of 4,350 c.c. The physical signs over the heart, and the blood pressure, were similar to those recorded previously. In spite of active therapy, the congestive heart failure did not improve, and the patient died June 28, 1938.



Fig. 5.—Case 2. The specimen shows the thickened right ventricle and the fistula into the pulmonary artery.

*Final Diagnoses.*—(1) Syphilitic aortitis involving the base of the aorta; (2) aneurysm of the ascending aorta; (3) aortic insufficiency(??); (4) fistula between the aortic aneurysm and pulmonary artery(?); (5) congestive heart failure, predominantly right-sided; (6) cardiac cirrhosis of the liver.

The autopsy was performed by Dr. Paul Kimmelstiel.

*Anatomic Diagnoses.*—(1) Right-sided hydrothorax, ascites, and edema; (2) collapse of the right lower lobe; (3) "nutmeg" liver, with beginning atrophic cirrhosis; (4) fistulous opening between an aortic aneurysm and the pulmonary artery (Fig. 5).

*Heart and Aorta.*—The heart was not weighed because the aorta, with the aneurysmal sac, was left attached to the heart.

*Measurements.*—Left ventricular wall, 1.5 cm.; right ventricular wall, 0.8 cm.; pulmonary ring, 7.0 cm.; aortic ring, 8.0 cm.; mitral ring, 12.0 cm.; tricuspid ring, 11.0 cm.

The heart was enlarged and its apex rounded, and the epicardium was smooth, moist, and glistening. Both ventricles were dilated and the walls hypertrophied, the right ventricle much more so than the left. The papillary muscles of the left ventricle and the trabeculae carneae were somewhat flattened; those in the right ventricle were markedly rounded and hypertrophied. The endocardium appeared normally firm, and free from foci on the cut surface. A rough, ante-mortem thrombus was found in the left auricular appendage. The commissures and valve leaflets of all cusps and valves appeared normal and delicate. The chordae tendineae appeared to be normal. The right coronary ostium was slightly narrowed by changes in the aortic wall, but the ostium of the left coronary artery was normal. The lumina of both coronary arteries were patent throughout; the walls were elastic, and the intima showed slight arteriosclerotic changes.

The entire ascending aorta bulged out anteriorly into a saccular aneurysm, the diameter of which was approximately 10 cm. The intimal surface was irregularly roughened by numerous atherosclerotic plaques, and by extensive longitudinal wrinkling. The wrinkling and irregular thickening of the aortic wall were present in the arch of the aorta, and descended as far as the beginning of the abdominal aorta, at which point the change in the aortic wall stopped abruptly.

There was a fistula between the pulmonary artery and the aorta which measured approximately 0.7 cm.; it was circular, and almost punched out in appearance. It was situated approximately 3 cm. from the aortic ring and 1.5 cm. above the pulmonary ring. There were two areas of scarring in the pulmonary artery next to the fistula, one immediately to the left of the opening of the fistula, and the other approximately 1 cm. to the right of the fistula; both scarred areas measured approximately 1 cm. in diameter and were irregular in outline.

CASE 3.—G. W., aged 58 years, a negro truck driver, was admitted to St. Philip Hospital Sept. 3, 1940.

*History.*—Approximately three weeks previously, his illness began with breathlessness which was sudden in onset and progressive in intensity. One week before he entered the hospital, dyspnea became so severe that he remained in bed in an orthopneic position, but with only partial relief. There had been no cardiac or thoracic pain, and only a mild, nonproductive cough. Swelling of the ankles was first noticed two weeks previously, and for one week the abdomen had been swollen and tender. His previous health had been normal except for a dry cough of five weeks' duration, accompanied by hoarseness and difficulty in swallowing; he attributed this to a "cold." Nothing significant was revealed in the past history or family record.

*Physical Examination.*—The patient was a well-nourished and well-developed man in an orthopneic position. There was no cyanosis. The temperature was 99° F.; the pulse rate, 105; and the respiratory rate, 31 per minute. The pupils were equal, and their reaction was normal. The arteries of the fundi showed a moderate degree of arteriosclerosis. The ears, throat, and mouth were not unusual. The patient was hoarse and his cough was brassy in quality, suggesting recurrent laryngeal nerve paralysis and tracheal compression. The neck veins were distended 4 cm. above the jugular bulb in the orthopneic position. The thorax was normal in shape, and was resonant except over the right base, where the percussion note was dull. A few medium, moist râles were heard over the lower lung lobes posteriorly,

and the breath sounds over the hilar area were high pitched; both inspiration and expiration were moderately prolonged, suggesting bronchial compression. In the right second and third intercostal spaces there was a visible and palpable pulsation. There was a definite increase in supracardiac dullness. The cardiac apex was seen and felt in the fifth intercostal space, and the left cardiac border was 13 cm. to the left of the midsternal line. The right cardiac border was not definitely located. Over the base of the heart, centering at the left third intercostal space, 3 cm. from the sternal margin, there was a purring systolic and diastolic thrill which was most distinct during the systolic phase. Over this same area there was a harsh, whirring, continuous murmur which was distinctly "cogwheel" in quality. The systolic phase was more intense and of longer duration than the diastolic. The diastolic murmur was transmitted only a few centimeters along the left sternal margin. There was no Austin Flint murmur. The aortic second sound was moderately accentuated and was amphoric in quality, and the pulmonic second sound was definitely accentuated. The pulse was rhythmic and typically Corrigan in type. The blood pressure was 190/50-40. The liver was tender and extended 8 cm. below the costal margin. There was edema of the sacral area and the lower extremities.

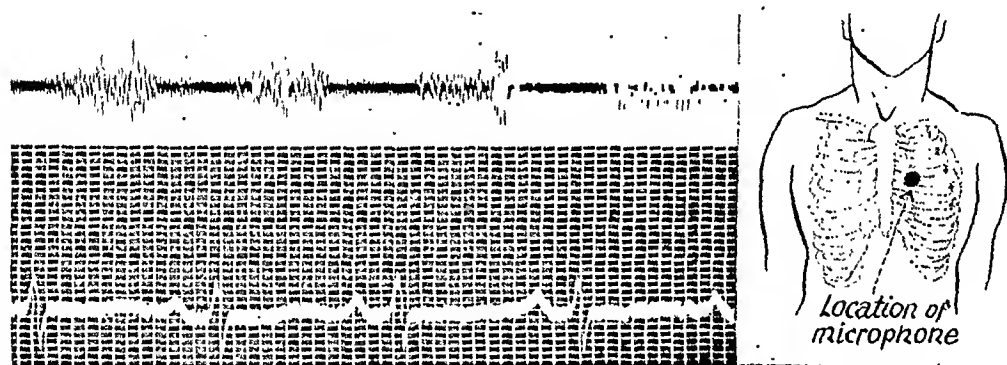


Fig. 6.—Case 3. Stethogram shows a continuous murmur with systolic accentuation.

*Laboratory Examination.*—The blood Wassermann and Kline reactions were positive. Examination of the blood showed: Hemoglobin, 69 per cent; erythrocytes, 3,900,000; leucocytes, 11,600; neutrophils, 70 per cent; lymphocytes, 18 per cent; monocytes, 10 per cent; and eosinophiles, 2 per cent. The urine was normal. Chemically, the blood was normal. Roentgenographic study: "A teleroentgenogram showed that the transverse diameter of the heart was 16.7 cm., and the transverse diameter of the thorax, 31 cm. The cardiothoracic ratio was 53 per cent. The transverse diameter of the great vessels was 14.2 cm. There were multiple saccular aneurysms of the ascending, transverse, and descending aorta. The saccular aneurysm, which was 7 cm. in diameter, at the right mediastinal margin showed a marked expansile pulsation. There were also saccular aneurysms of the transverse and descending portions. There were marked mottling of the vascular markings of both lungs and moderate pleural effusion at both costophrenic angles. Esophagrams showed pressure of the aneurysmal aorta on the esophagus. The lower half of the esophagus was flattened and displaced to the left and posteriorly. The kymogram showed expansile pulsation of several saccular aneurysms." Electrocardiographic study showed sinus tachycardia, rate 107; diphasic T in Leads I, II, and III, suggesting digitalis effects; left axis deviation; axis,  $-40$ . The stethogram showed a continuous murmur with a systolic accentuation (Fig. 6).

*Clinical Diagnoses.*—(1) Syphilitic aortitis with saccular aneurysms; (2) fistulous communication between aortic aneurysm and the pulmonary artery; (3) congestive

heart failure, predominantly right-sided; (4) tracheal compression, with atelectasis of the lower lobes of the lungs.

*Hospital Course.*—Digitalis, diet restrictions, and diuretics gave only partial relief. The venous pressure continued high, varying from 130 to 200 mm. of water. The edema of the lower extremities increased and bilateral pleural effusion developed but never became sufficiently large to require aspiration. Ascites did not develop. Orthopnea was continuous, and it was only partially relieved by oxygen therapy and opiates. Death occurred on Nov. 7, 1940, from respiratory difficulty and heart failure.

The autopsy was performed by Dr. John S. Howe.



Fig. 7.—Case 3. The specimen shows the slitlike opening into the pulmonary artery. (The specimen was mutilated through error.)




*Anatomic Diagnoses.*—(1) Atelectasis of the right lower lobe; (2) atherosclerosis of the aorta; (3) syphilitic aortitis; (4) passive congestion of the liver and kidneys; (5) hydrothorax on the right; (6) early stage of nutmeg liver; (7) fistulous opening between an aortic aneurysm and the pulmonary artery (Fig. 7).

*Heart and Aorta.*—The heart was moderately enlarged; the right ventricle was somewhat larger than the left. The left ventricular wall measured 2.2 cm., and the right ventricular wall, 1 cm., in thickness. The aortic valve ring was 7 cm. in circumference, and the pulmonic, 6.5 cm. The mitral, tricuspid, and pulmonic valve leaflets were thin and translucent. The aortic valve leaflets were thin and pliable, with sharp, free margins. There was slight separation of the aortic leaflets by a whitish translucent plaque at one commissure, and there was fusion of another commissure. There was partial fusion of two of the valve leaflets for a distance of 5 mm. from the commissures. The aorta just beyond the valve ring was diffusely dilated, and its intima showed marked longitudinal wrinkling, scarring, and whitish and yellowish translucent plaques. This diffuse dilatation involved the whole arch of the aorta to a point 12 cm. beyond the origin of the left subclavian artery. In ad-

dition to diffuse saccular dilatation of the arch of the aorta, there was a saccular dilatation which arose at a point 6.5 cm. above the aortic ring and communicated by a narrow ostium, 3.5 cm. in diameter, with the aorta. In this saccular dilatation, which was anterior to the aorta and on the posterior surface of the pulmonary artery, there was a slitlike perforation 1 cm. in length and 2 mm. in width. This opened into the pulmonary artery at a point 4.5 cm. above the pulmonic valve ring. There was another, smaller, saccular aneurysm at the transverse part of the arch, lying above the arch of the aorta. Its opening measured 3 cm. in diameter, and from it arose the innominate artery and the left common carotid artery. The left subclavian arose from the main aorta at a point 1.5 cm. beyond the opening of this saccular aneurysm.

COMMENTS

Opinions concerning the prognosis of rupture of an aortic aneurysm into the pulmonary artery have been eharacterized by great variation. Osler and McCrea,<sup>11</sup> in discussing the complications of aortic aneurysm, said: "The sack may rupture into the pulmonary artery, producing instantaneous death." On the other hand, Clere, et al.,<sup>12</sup> reported a patient who supposedly lived for more than four years.

| <u>CASE<br/>NUMBER</u> | <u>AGE</u> | <u>LOCATION OF ANEURYSM</u>   | <u>SIZE AND SHAPE<br/>OF FISTULA</u>   | <u>DURATION OF ILLNESS</u> |
|------------------------|------------|---|--|----------------------------|
| 1.                     | 55         | ascending aorta   | <br>1 x 1.2 cm.    | 4 wks., +- days            |
| 2.                     | 50         | ascending aorta   | <br>0.7 cm.       | 8 mos., +- days            |
| 3.*                    | 58         | multiple large<br>aneurysms of as-<br>cending and<br>transverse aorta | <br>1 cm. x 2 mm. | 2 mos., +- days            |

\*Complicated by essential hypertension

Fig. 8.

It is apparent that each case is a specific problem, for the factors which decide the duration of life are the size and the number of aneurysms, the size of the fistulous opening, the extent of the assoeiated cardiovascular disease, and the effieieney of the therapy. Fig. 8 attempts to summarize these factors as they concern the cases here reported. It is significant that in Case 2 the patient was relieved of all aetive symptoms for a period of approximately six months. In this case the location and size of the aneurysm were such that it did not eompress any vital mediastinal structure; the fistulous opening was of moderate size (0.7 em. in diameter), and there was no eomplicating eardiovascular disease.

At autopsy, right ventricular hypertrophy and dilatation were strik- ing in each of the three cases here reported. Stevenson found marked

hypertrophy in two cases and a normal right ventricle in a third case. In the two cases in which there was right ventricular enlargement, the fistulous opening was "large," whereas, in the third case, in which there was no enlargement of the right ventricle, the opening was "very small." In the case reported by Peacock, there was, in addition to the fistulous opening into the pulmonary artery, disease of the aortic valve which he concluded resulted in aortic regurgitation. In commenting on the size of the heart, he emphasized the fact that the enlargement of the right ventricle was greater than is usually found in uncomplicated aortic regurgitation.

An explanation for the stress which results in right ventricular enlargement is obscure and cannot be finally ascertained without carefully controlled animal experiments. It would seem obvious that a fistulous connection between the aorta and the pulmonary artery would result in a great increase in the pressure in the pulmonary artery; yet the observed facts do not bear out this conclusion. Blalock<sup>13</sup> and his associates have anastomosed the subclavian artery to the pulmonary artery in dogs, and in this experiment there was no rise of the pressure in the pulmonary artery. It is safe to predict that there can be a very great increase in the minute volume of blood passing through the lesser circulation without a corresponding rise in pulmonary arterial pressure, provided the left ventricle remains efficient. In the above experiment the current of blood from the subclavian artery entered the pulmonary artery in the direction of the pulmonary blood flow; and, if a current of blood is shunted from the aorta, a high pressure tube, into the pulmonary artery, a low pressure tube, in the direction of the pulmonary current, the pressure proximal to the point of entrance is reduced by the suction effect of the high tension current. On the other hand, if the current from the aorta enters at a right angle to the pulmonary current or is directed toward the right ventricle, an increase in pressure proximal to the fistula would result, and the right ventricle would be required to overcome this. It is quite probable that this hydrodynamic factor is the major one in connection with the enlargement of the right ventricle.

Pressure of the aneurysmal sac on the pulmonary artery, reducing its lumen, could increase the resistance to blood flow in the pulmonary artery, and result in increased right ventricular stress. The patient in Case 2 had the most striking degree of right ventricular enlargement, and the electrocardiogram strongly indicates that this developed after the establishment of the fistulous connection. Furthermore, in the cases reported by Stevenson, there was a definite relationship between the size of the opening and the size of the right ventricle.

The factors responsible for an increase in the size of the myocardium remain debatable; yet, a continuous increase in work, relative or absolute,



beyond a critical level, is the one constant factor which is found in all instances of acquired heart muscle hypertrophy. In the cases under discussion, many factors may have been concerned, but it is more than probable that the effects of the current of blood from the aorta on the pressure in the pulmonary artery proximal to the fistulous opening were the essential ones. That stress on the right ventricle existed is evidenced not only by the pathologic changes, but by the preponderance of right-sided heart failure which was such a striking feature in these cases.

Continuous and severe breathlessness was a prominent clinical feature, but observation did not indicate that pulmonary stasis (left ventricular failure) was the cause of the dyspnea and accelerated rate of respiration. In all of the cases there were basal râles, but it must be emphasized that the extent of pulmonary stasis was strikingly slight, considering the intensity of the dyspnea. Furthermore, oxygen in high concentration modified the breathlessness very little, if at all.

The establishment of a fistulous connection between the aorta and the pulmonary artery results in a great increase in the minute volume of blood passing through the pulmonary arterial tree. The magnitude of the augmented circulating volume is directly related to the size of the fistula, but it is a certainty that, as a result, there are varying degrees of engorgement of the afferent vessels, including the afferent arterioles and alveolar capillaries.

The primary stimulus of the Hering-Breuer reflex is the tension change in the lung parenchyma; and any condition, such as pulmonary engorgement, will increase the sensitivity of this reflex, resulting in rapid breathing, with dyspnea. The type of respiration and the continuous breathlessness observed in these cases suggest that this reflex mechanism is the essential factor, rather than pulmonary edema resulting from failure of the left ventricle.

The diagnosis of rupture of an aortic aneurysm into the pulmonary artery is an intriguing clinical problem. It is difficult to ascertain from a review of the reported cases how often this has been accomplished, for, in most instances, the authors do not make a definite statement. It is obvious that the probability of a correct clinical diagnosis may be influenced by many factors. The cases here reported may be a fair sample of what one might expect in others; nevertheless, it is reasonable to assume that such factors as the size of the fistula, pressure from the aneurysms, and associated cardiovascular disease could very definitely modify the clinical course.

A study of these cases shows that the symptoms and signs are characteristic. Syphilitic aortitis, with aortic regurgitation, is the one cardiac lesion which must be seriously considered in the differential diagnosis.

The similarity becomes less confusing when the entire syndrome is summarized, as follows:

1. Continuous and severe breathlessness.
2. The physical signs of pulmonary stasis which are slight in proportion to the intensity of the dyspnea.
3. Preponderance of right-sided heart failure, which develops immediately after the onset of the acute respiratory distress.
4. Cyanosis, which is not a significant phenomenon.
5. A purring systolic and diastolic thrill over the base of the heart, most intense during the systolic phase.
6. A long, harsh, continuous murmur, with the point of maximum intensity at the third intercostal space, 1 to 3 cm. to the left of the sternal margin. The systolic phase of the murmur is peculiarly harsh and long, whereas the diastolic phase is short in duration, and is transmitted downward for only a few centimeters along the left sternal margin. The murmur is best heard with the patient in a sitting posture and leaning slightly forward.
7. Absence of an Austin Flint murmur.
8. The peripheral arterial manifestations of free aortic insufficiency.
9. Physical and roentgenographic evidence of aneurysm of the ascending aorta.
10. Cardiac enlargement, but not classically aortic in type.
11. The electrical axis of the heart which may progress to right axis deviation.
12. A murmur which is similar in its essential details to that in cases of patent ductus arteriosus, as shown in the stethogram.

#### SUMMARY AND CONCLUSIONS

1. Three cases of aortic aneurysm opening into the pulmonary artery are reported. From a study of these cases the syndrome accompanying this complication of aortic aneurysm is constructed.

2. A tentative explanation is offered for the stress on the right ventricle which results in right ventricular hypertrophy and dilatation, and the occurrence of right-sided heart failure soon after the establishment of the fistula.

This complication of aneurysm of the aorta was correctly diagnosed by Dr. White<sup>14</sup> and his associates eight months before the death of a 72-year-old patient who was studied by them.

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# A SIMPLE, INDIFFERENT, ELECTROCARDIOGRAPHIC ELECTRODE OF ZERO POTENTIAL AND A TECHNIQUE OF OBTAINING AUGMENTED, UNIPOLAR, EXTREMITY LEADS

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## INTRODUCTION

ELECTROCARDIOGRAMS obtained with standard leads represent, in reality, a combination of two graphs, one from each of the extremities being utilized.<sup>1</sup> The standard limb leads are, therefore, bipolar extremity leads. It would therefore seem plausible that electrocardiograms which represent the potential variations of only one region of the body would lend themselves to interpretation and analysis more readily than the standard lead electrocardiograms. Such is practically the case when precordial leads are used. However, in order to obtain unipolar extremity leads (electrocardiograms that represent the potentials of only *one* extremity), special apparatus, more or less complicated, has been required. In one of the methods<sup>2</sup> the patient is immersed in a water bath. Another technique, devised by Wilson et al.,<sup>3</sup> is less complicated; the extremities are connected to a central terminal through fixed resistances of 5,000 ohms each.

Recently we have been making a study of extremity potentials (using a Wilson assembly), and, in the course of our work, devised a simple indifferent electrode of zero potential (which can be constructed in a few minutes at a cost of less than 10 cents) and a technique of obtaining "augmented" unipolar extremity leads.

## CONSTRUCTION OF THE INDIFFERENT ELECTRODE

Three single lengths of ordinary electric wire and four battery clips are needed. The wire should be approximately 4 feet in length. (1) Take the three lengths, expose their ends, join as in Fig. 1, and apply one of the clips. (2) To the other ends of the wires tips can be soldered, the other battery clips attached, or such attachments made as are necessitated by variations in the construction of the electrodes of different kinds of electrocardiographs.

## TECHNIQUE OF OPERATION

*Precordial Leads.*—(1) Set the lead switch for Lead I. (2) Place electrodes on the patient's right and left forearms and left leg, using a suitable jelly or paste on

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the skin. (3) Attach the indifferent electrode as illustrated in Fig. 2. (4) Attach the *RA* lead wire (from electrocardiograph) to the central terminal, *T*. (5) Attach the *LA* lead wire to the precordial electrode and apply where desired. (6) Standardize the electrocardiogram in the usual manner and make the record. In the

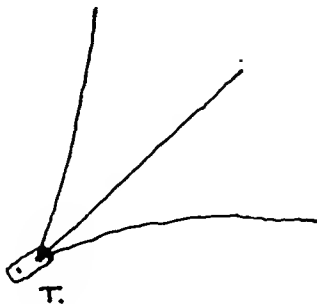


Fig. 1.—Three single lengths of ordinary (No. 18) electric wire, joined to form an indifferent electrode of zero potential. *T*, Central terminal.

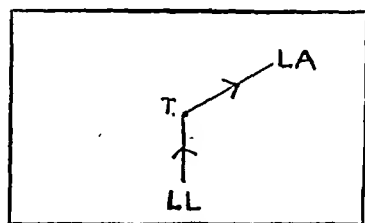
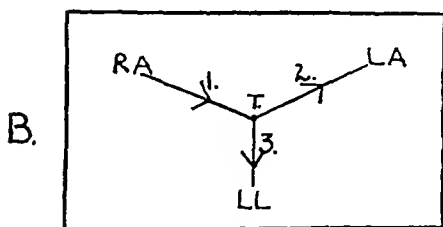
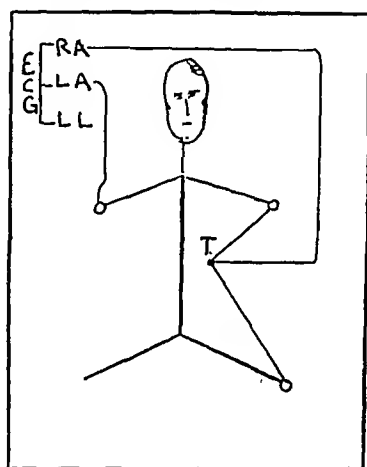
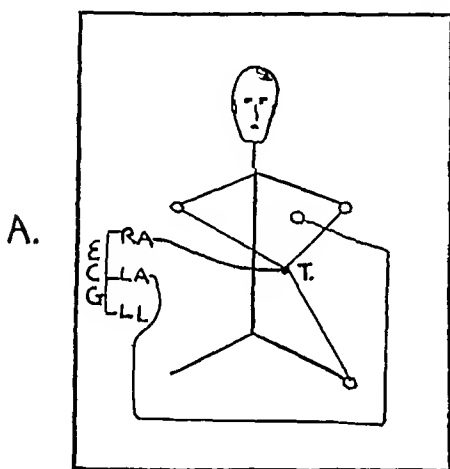


Fig. 2.

Fig. 3.

Fig. 2.—*A*, Indifferent electrode connected to take a precordial lead. (The electrocardiograph is set for Lead I.) Wilson's or the author's indifferent electrode may be used. *B* illustrates the hypothetical current flow through the indifferent electrode at a given instant. The arrows indicate direction of current flow.

Fig. 3.—*A*, Indifferent electrode connected to take the "augmented" right arm lead (the *aVr* lead). The electrocardiograph is set for Lead I. The author's or Wilson's indifferent electrode may be used. *B* illustrates the hypothetical current flow through the indifferent electrode at a given instant. The third end of the indifferent electrode (not drawn) is left free.

finished record, positivity will be denoted by an upward deflection, as recommended by the American Heart Association. If the switch is set for Lead II, connect the *LL* lead wire instead of the *LA* lead wire to the precordial electrode. If the switch is set for Lead III, connect the *LA* lead wire instead of the *RA* lead wire to the central terminal, and the *LL* lead wire to the precordial electrode.

For unipolar extremity leads two techniques are available,

### A. Augmented Unipolar Extremity Leads

*“Augmented” Right Arm Lead (aVr Lead).*—(1) Set the switch for Lead I. (2) Place electrodes on the patient's right and left forearms and left leg. (3) Attach the indifferent electrode as illustrated in Fig. 3. (4) Attach the *RA* lead wire to the central terminal. (5) Attach the *LA* lead wire to the electrode on the right forearm. (6) Standardize the electrocardiogram as usual, and make the record. In the finished record, positivity will be represented by an upward deflection, and, despite the standardization, 1.5 cm.  $\equiv$  1.mv. (see below for explanation).

To record the “augmented” left arm lead (aVl lead), connect two ends of the indifferent electrode to the electrodes on the right forearm and left leg (the third end of the indifferent electrode is left loose).

To take the “augmented” left leg lead (aVf lead), attach the indifferent electrode to the electrodes on the right and left forearms.

*With this technique for augmented unipolar extremity leads, always leave the indifferent electrode off the extremity being recorded.*

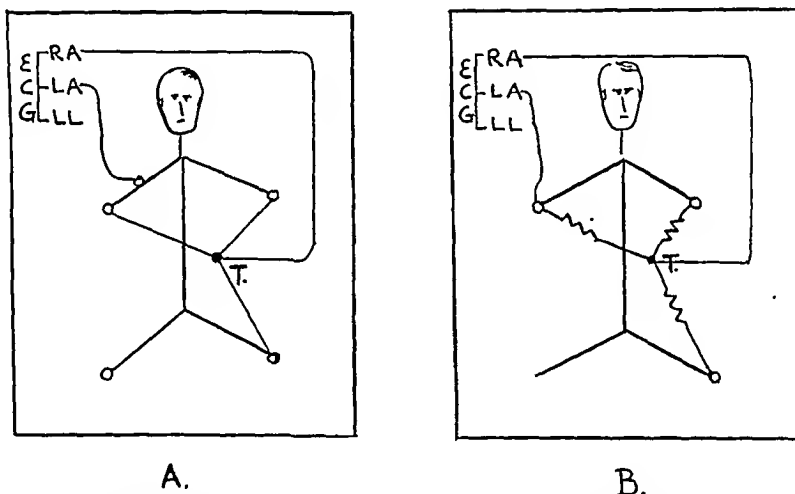


Fig. 4.—A, The author's indifferent electrode, connected to take the ordinary right arm lead, *Vr*. (A fourth electrode is placed on the right arm.) B, Wilson's indifferent electrode, connected to take the ordinary right arm lead, *Vr*.

### B. Ordinary Unipolar Extremity Leads

*Ordinary Right Arm Lead (Vr).*—(1) Set the switch for Lead I. (2) Place the electrodes on the right and left forearms and the left leg. (3) Place a fourth electrode on the patient's right arm near the elbow. (4) Attach the indifferent electrode as for precordial leads (Fig. 4A). (5) Attach the *RA* lead wire to the central terminal. (6) Attach the *LA* lead wire to the fourth electrode on right arm near the elbow. (7) Standardize as usual. In the finished record, positivity will be represented by an upward deflection.

To take the ordinary left arm lead (*Vl*), attach the fourth electrode near the left elbow and proceed as above.

To record the ordinary left leg lead (*Vf*), attach the fourth electrode near the left knee, and proceed as above.

With this technique, the records are similar to those obtained and described by Wilson, et al.,<sup>13</sup> and Kossmann, et al.<sup>4</sup>

## DISCUSSION

In order to understand the operation of the author's indifferent electrode, the following presentation of the electrical principles underlying the use of an indifferent electrode of this type is necessary.

When the extremities are joined, as in Fig. 2, to record precordial potentials, the current flow,  $I$ , through the circuit may be determined by Kirehnhoff's law, namely, that the total current flowing out of a central point is equal to the total current flowing into it. Thus, if the current flow at a given instant is as indicated by the arrows in Fig. 2B,

$$(1) \quad I_1 = I_2 + I_3$$

$$\text{or} \quad \frac{E_{RA} - E_T}{R_1} = \frac{E_T - E_{LA}}{R_2} + \frac{E_T - E_{LL}}{R_3}$$

If the resistances are equal, the potential at the central point,  $T$ , is equal to the mean potential of the extremities to which it is joined. The proof of this is as follows. Since the resistances are considered equal,\* equation (1) may be rewritten

$$RA - T = T - LA + T - LL$$

$$\text{or} \quad 3T = RA + LA + LL$$

$$T = \frac{RA + LA + LL}{3}$$

Since it has been demonstrated<sup>1</sup> that the sum of the extremity potentials equals zero (i.e.,  $RA + LA + LL = 0$ ),

$$T = 0$$

On study of this problem, we felt that the introduction of external resistances might not be necessary in view of the fairly high skin-electrode resistances, and experiments were conducted along these lines, using ordinary (No. 18) electric wire to connect the extremities (Fig. 1). The results were very satisfactory.

Carrying the theoretical analysis further, as was pointed out above, Wilson employed the fixed external resistances in order to equalize the inequalities of skin resistance. However, it must be realized that, although with this technique the differences between the total resistances become proportionately less, they still are not equal. A major objection to our technique, however, might be that the use of low-resistance wires joining the extremities (through the central terminal) would effect a decrease in the potentials at the extremities, and a marked alteration in the electrical field around the heart. In order to ascertain whether this was so, we studied the effects of shunts (connecting the extremities) on the configuration of standard leads, in the following way. The subject was a 58-year-old woman who had suffered an attack of myocardial infarction five weeks previously.

\*It was to approach this condition, and thus obviate the effects of the inequalities of skin-electrode resistances,† that Wilson, et al.,<sup>3</sup> placed fixed resistances of 5,000 ohms between each extremity and the central terminal.

†It would be more correct to say "resistance from the electrode to the source of potential."

*Experiment 1.*—(1) Lead II was taken in the usual way, with electrodes on the volar surface of the right wrist and the lateral aspect of the left leg, just above the ankle (Fig. 5*A*). (2) Two additional electrodes were placed on extremities, one on the volar aspect of the right arm, 3 inches above the original electrode, and the other on the lateral aspect of the left leg, 4 inches above the original. Control Lead II was taken (Fig. 5*B*). (3) Low-resistance (No. 18) wire was connected to the electrode on the left arm and the proximal electrodes on the right arm and left leg (the author's indifferent electrode was used). Lead II was taken (Fig. 5*C*). (4) The Wilson assembly was connected (as a control) as in No. 3; Lead II was taken (Fig. 5*D*).

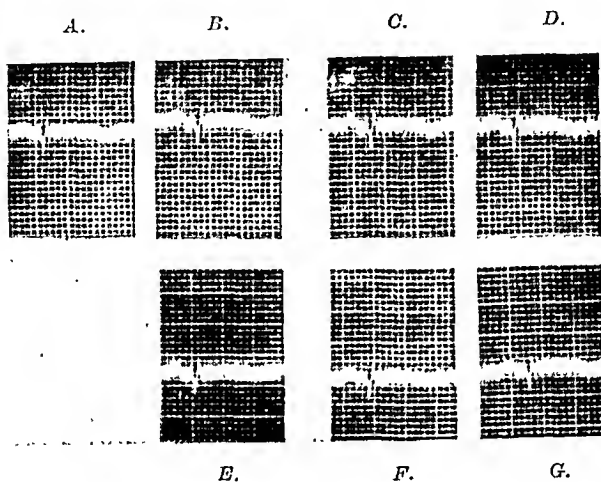


Fig. 5.—*A*, Lead II, taken with electrodes on the volar surface of the right wrist and the lateral aspect of the left leg just above the ankle. *B*, Control Lead II, after the additional electrode was placed on the volar aspect of the right arm, 3 inches above the original, and on the lateral aspect of the left leg, 4 inches above the original. *C*, Lead II after a low-resistance shunt was connected to the proximal electrodes of the right arm and left leg. *D*, Lead II after a Wilson assembly was connected to the proximal electrodes of the right arm and left leg. *E*, Lead II, taken with four electrodes on the right arm and left leg, connections being made with the proximal electrodes. *F*, Lead II after a low-resistance shunt was connected to the distal electrodes of the right arm and left leg. *G*, Lead II after a Wilson assembly was connected to the distal electrodes of the right arm and left leg.

*Experiment 2.*—(1) With the four electrodes on the right arm and left leg, the connection for Lead II was made with the proximal electrodes; control Lead II was taken (Fig. 5*E*). (2) Low-resistance shunts were connected to the distal electrodes on the right arm and left leg, and to the left arm; Lead II was taken (Fig. 5*F*). (3) The Wilson assembly was connected as in step 2 (for control); Lead II was taken (Fig. 5*G*).

## RESULTS

Since the limbs are considered as linear extensions of points at the apices of an equilateral triangle inscribed in a spherical volume conductor,<sup>5</sup> a decrease of potential at any point on the extremity should be reflected along the extremity, especially at points distal to the region where the potential has been decreased. The above experiments showed absolutely no demonstrable change in the configuration of Lead II when the extremities were shunted with low-resistance wire. The reason for this is that the usual skin-electrode resistance is sufficiently high to prevent a marked drop in potential when the extremities are joined, even



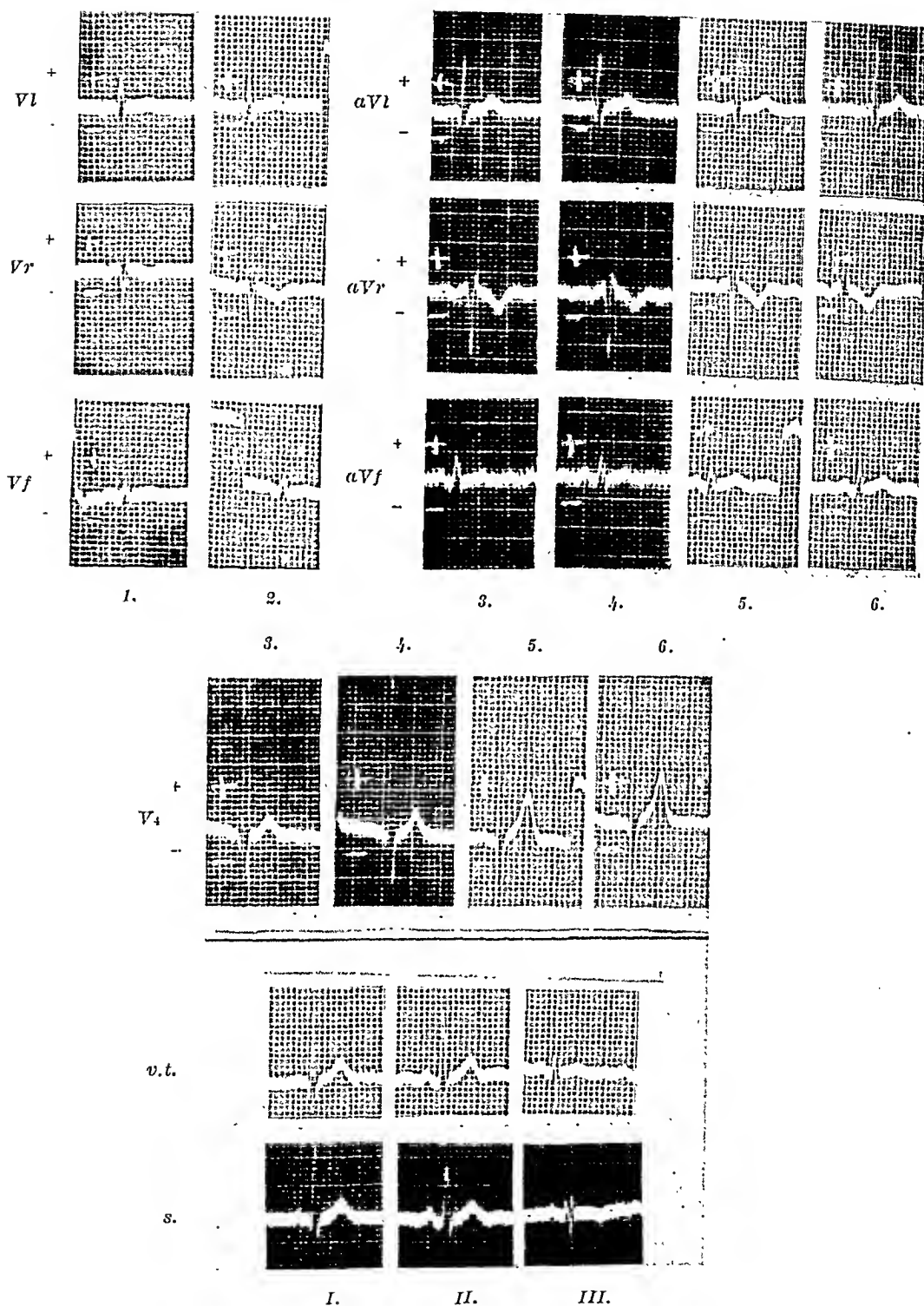


Fig. 6.—Comparison of unipolar extremity, and precordial leads taken with different techniques. Subject ♂ 28, normal. *VI*, ordinary left arm lead; *Vr*, ordinary right arm lead; *Vf*, ordinary left leg lead; *aV1*, the *aV1* lead (the augmented left arm lead); *aVr*, the *aVr* lead (the augmented right arm lead); *aVf*, the *aVf* lead (the augmented left leg lead); *V4*, precordial lead, with electrode at 5 i.c.s., mid-clavicular line; *v.t.*, standard leads taken with vacuum tube type of electrocardiograph; *s.*, standard leads taken with string galvanometer electrocardiograph; 1, ordinary unipolar extremity leads taken with string electrocardiograph and Wilson assembly; 2, ordinary unipolar extremity leads taken with vacuum tube electrocardiograph and Wilson assembly; 3, augmented extremity, and precordial, leads taken with a string electrocardiograph and Wilson assembly; 4, augmented extremity, and precordial, leads taken with a string electrocardiograph and the author's indifferent electrode; 5, augmented extremity, and precordial, leads taken with vacuum tube electrocardiogram and the author's indifferent electrode; 6, augmented extremity, and precordial, leads taken with vacuum tube electrocardiograph and the Wilson assembly.

through a low-resistance circuit. However, this is not to deny that there is a current flow of magnitude through the low-resistance wire, because, if it were to be connected directly to the two electrodes taking the standard lead, no deflection of the string could be obtained. (This is the reason for using a fourth electrode when ordinary unipolar extremity leads are taken.)

We have used the author's indifferent electrode in more than 1,500 cases; and in approximately 100 of these we also made not only precordial, but the unipolar extremity, leads with the Wilson assembly for comparison. This latter series comprised normal subjects and patients with abnormal auricular patterns, myocardial infarction with both  $Q_1$  and  $Q_3$  patterns, bundle branch block and interventricular conduction disturbances, and digitalis effects.

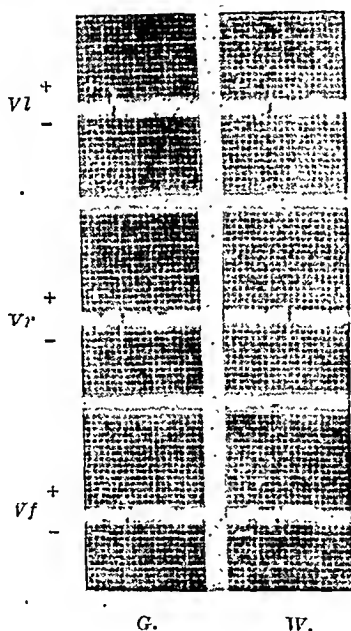


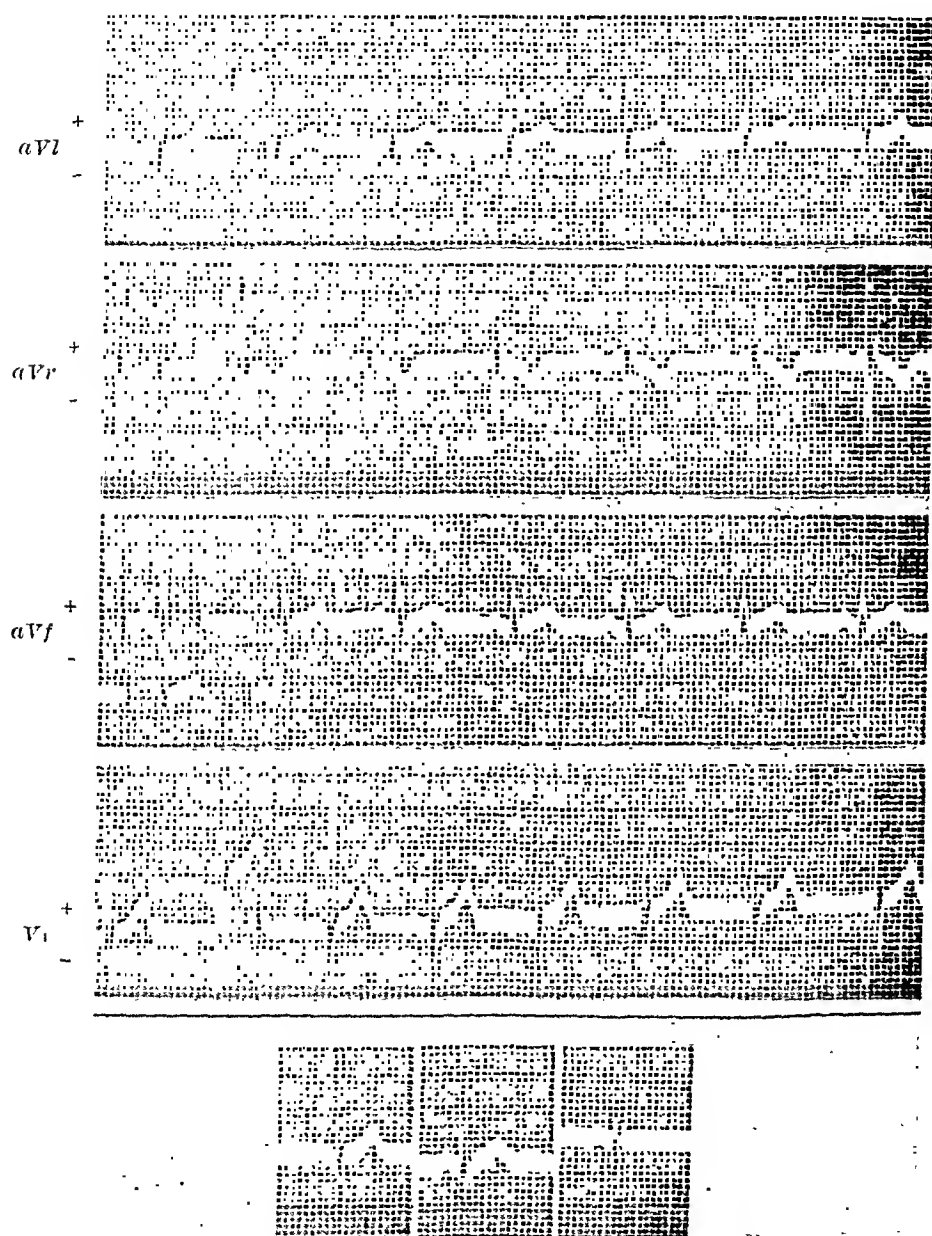
Fig. 7.—Comparison of ordinary unipolar extremity leads taken with the author's and with Wilson's indifferent electrode. *G*, Leads taken with the author's indifferent electrode; *W*, leads taken with the Wilson assembly.

Fig. 6 shows precordial Lead  $V_4$  from a normal subject, taken with the author's indifferent electrode, with the Wilson assembly, and with a string, and a vacuum tube, type of electrocardiograph.

To conclude, for purposes of clinical electrocardiography, precordial leads taken with the author's or Wilson's indifferent electrode, using a string or a vacuum tube electrocardiograph, may be considered identical. When ordinary unipolar extremity leads are taken with the author's indifferent electrode, a fourth electrode must be placed on the extremity from which the record is being recorded, for reasons explained above. Fig. 7 shows the ordinary unipolar extremity leads, taken with the author's and Wilson's indifferent electrodes, in a case of myocardial infarction.

THE USE OF AN INDIFFERENT ELECTRODE TO OBTAIN "AUGMENTED"  
UNIPOLAR EXTREMITY LEADS

Realizing that extremity leads, as ordinarily taken, are of small amplitude, we devised the technique described above in order to augment the amplitude of the unipolar extremity leads. *The technique,*



I. II. III.  
Fig. 8.—Subject ♂ 29, normal.

in essence, is that the indifferent electrode is kept off the extremity from which the record is being recorded. The proof of the validity of our technique is as follows. If the augmented right arm lead is being taken (Fig. 3), the potential at the central terminal,  $T$ , is equal to

$$\frac{LA + LL}{2} \text{ or } \frac{-RA}{2}$$

$$\begin{aligned} \text{Since } RA + LA + LL &= 0 \\ LA + LL &= -RA \\ \text{and } \frac{LA + LL}{2} &= \frac{-RA}{2} \end{aligned}$$

The record so obtained would be equivalent to  $RA - (-\frac{RA}{2})$  or  $\frac{3}{2} RA$ .

It is for this reason that we have called the unipolar extremity records obtained with this technique augmented unipolar extremity leads. The augmented left arm and left leg leads may be similarly analyzed.

It may be pointed out that the augmented left leg potential is approximately equal to  $E \sin \alpha$ , where  $\alpha$  is the angle made by the electrical axis with that side of Einthoven's triangle which corresponds to Lead I and  $E$  is the manifest potential. This is so because the potential of the unaugmented left leg lead equals  $\frac{E \sin \alpha}{\sqrt{3}}$  ( $\sqrt{3} = 1.73$  approx.).<sup>6</sup> As

was mentioned above, just as for the precordial leads, we compared augmented unipolar extremity leads taken with the author's and Wilson's indifferent electrodes in a similar series of cases, and obtained identical results. Fig. 6 illustrates this in a normal subject.

To the augmented unipolar lead derived from the right arm we have given the name, the aVr lead. The term aVl lead indicates the augmented left arm lead. The augmented left leg lead is known as the aVf lead.\* This distinguishes them from the ordinary unipolar extremity leads which are known as Vr, Vl, and Vf, respectively.<sup>3</sup>

#### CONCLUSIONS

When precordial leads are being recorded, the use of an indifferent electrode of the type described above is predicated on the concept that, when the extremities are connected to a central terminal, the potential at this central point equals zero. Theoretically, this holds only when all resistances are equal. However, for purposes of clinical electrocardiography, it is not necessary to equalize the resistances of the circuit by the introduction of fixed resistances (the Wilson assembly); the three extremities may be joined to a central terminal with ordinary electric wire, and the Wilson assembly and the author's indifferent electrode may be used interchangeably in the recording of precordial leads.

When ordinary unipolar extremity leads are being recorded with the author's indifferent electrode, a technique slightly different from that used with the Wilson indifferent electrode must be employed (Fig. 4).

\*The characteristics of these leads in both normal and abnormal subjects will be presented elsewhere. Fig. 8, from our records, illustrates how we file these leads.

However, we have, in our studies of unipolar extremity potentials, discarded the ordinary unipolar extremity leads and use a technique in which augmented unipolar extremity leads are obtained. Essentially, our technique consists in *not* connecting the extremity from which the electrocardiogram is being recorded to the central terminal; the other two extremities are so connected. It is immaterial whether the author's or Wilson's indifferent electrode is used, with either a string or vacuum tube electrocardiograph. We have designated the augmented unipolar extremity leads obtained with our technique as follows: (1) the aV<sub>r</sub> lead, which records potentials from the right upper extremity; (2) the aV<sub>I</sub> lead, which records potentials from the left upper extremity; (3) the aV<sub>f</sub> lead, which records potentials from the left lower extremity.

#### SUMMARY

1. The construction of a simple indifferent electrode of zero potential is described.
2. Theoretical and experimental evidence of its efficiency is presented.
3. A technique for obtaining augmented unipolar extremity leads is described.

The author wishes to thank Dr. Frank N. Wilson, of Ann Arbor, Mich., for his helpful suggestions in the preparation of the manuscript, and Dr. Samuel Alpert, of New York, who took several of the electrocardiograms used in this study.

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# LUMBAR SYMPATHECTOMY IN THE TREATMENT OF PERIPHERAL ARTERIOSCLEROTIC DISEASE

## II. GANGRENE FOLLOWING OPERATION IN IMPROPERLY SELECTED CASES

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IN A RECENT communication<sup>1</sup> criteria were presented for the selection of cases of peripheral arteriosclerotic disease in which lumbar sympathectomy is indicated, together with a résumé of the results obtained in a group of twelve such patients who had been observed for a period of a year, or longer, after operation. This original series has now been extended to include twenty-eight arteriosclerotic lower extremities in which sympathectomy was considered advisable. The results obtained in the entire group have been uniformly encouraging. It will be recalled that this group was a highly selected one and included only those cases in which preoperative examination revealed the presence of a healthy collateral arterial circulation and a flexible peripheral arteriolar bed, but in which sympathetic constrictor impulses to the latter frustrated all attempts at conservative vasodilating therapy.

The necessity of being circumspect in the selection of cases of peripheral arteriosclerotic disease for lumbar sympathectomy cannot be over-emphasized. The suggested criteria must be strictly adhered to, lest not only disappointing, but, in some instances, disastrous, results ensue. It has been personally observed that, in a certain type of arteriosclerotic extremity, sympathetic denervation of the foot is followed by gangrene. Preoperative clinical observation indicates that this untoward result is likely to follow when the disease process, by virtue of its location or its extent, has blocked or obliterated the collateral circulation. In such instances the nutrition of the foot is precariously maintained by the seepage of blood through partially occluded, diseased channels which can neither dilate nor hypertrophy in response to a surgically induced reduction of peripheral resistance to blood flow. A rapid onset of gangrene after lumbar sympathectomy has been personally encountered on three occasions. Despite the absence of an effective collateral circulation, the distal arteriolar beds remained flexible, as was indicated by a measurable rise in the surface temperature of all three feet, after sympathectomy, to vasodilatation levels 2° to 5° C. higher than were anticipated from preoperative studies. However, for reasons which will shortly become

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apparent, this rise in skin temperature was deceptive. In these cases there were other definite and readily recognized characteristics. Oscillometric readings at the supramalleolar level were zero in all three. Extreme pallor of the foot on elevation, with rubor or cyanosis on dependency, was present in all three. Conspicuous atrophy of the skin and subcutaneous tissue was observed in two. Finally, the filling time of the emptied dorsal venous arches was prolonged well beyond thirty seconds in all three feet.<sup>2</sup>

The mechanism whereby lumbar sympathectomy apparently expedited tissue necrosis in these cases is somewhat obscure. It cannot be accounted for by sudden thrombosis of a previously patent major vessel for several reasons. (1) The only major artery in which a pulsation could be felt preoperatively in any of these extremities was the femoral; pulsation in the femoral, when it was present preoperatively, remained undiminished until the time of amputation. (2) The onset of gangrene was not acute, and its development was slowly progressive. (3) The gangrene was patchy in its distribution, and the intervening tissue remained healthy until the time of amputation. (4) Except for one case in which the femoral and popliteal arteries had become acutely thrombosed preceding the sympathectomy, pathologic examination of the arteries did not reveal evidence of a recent thrombosis.

A consideration of the part played by the arteriovenous anastomoses in the presence of serious obstruction to the flow of blood to the foot may illuminate the problem. Popoff<sup>3</sup> suggested, and Harpuder and his co-workers<sup>4</sup> presented experimental evidence, that, in the presence of peripheral vascular disease, the arteriovenous anastomoses which are distributed throughout the foot may shunt a significant quantity of blood directly into the venous circulation before it has the opportunity of reaching the capillary bed, where it would be available for cellular nutrition. In the light of this evidence, it is not inconceivable that, in the presence of a rigidly impaired blood supply, surgically induced relaxation of patent and flexible arteriovenous anastomoses in an ischemic foot could shunt blood from the capillary beds in sufficient quantity to cause tissue necrosis and gangrene. Since surface temperature is apparently controlled by the volume rate of blood flow through these arteriovenous shunts, an explanation is thus available for the fact that a foot may become warm and also gangrenous as a direct result of sympathectomy.

#### CASE REPORTS

CASE 1.—A 61-year-old white man gave a history of intolerable, constant pain in his right foot, accompanied by subjective sensations of coldness. Intermittent claudication on the slightest exertion was likewise present. The symptoms had begun three years previously and had progressively increased in severity.

*Examination.*—Oscillometric examination revealed absence of pulsation in the lower part of the leg. A pulsation was palpable in the femoral, but not in the popliteal, posterior tibial, or dorsalis pedis arteries. The venous filling time was sixty seconds. There was extreme pallor of the foot on elevation, with cyanosis and rubor on dependency. The skin of the foot was very cold to the touch and was atrophic; neither ulceration nor gangrene was present. Immersion of the foot in a whirlpool bath at a temperature of 95° F. produced intense cyanosis and an increase in the pain.

Lumbar sympathectomy was performed in an attempt to relieve the pain. Within twenty-four hours the foot became palpably warm, but the pain was not relieved. Within two weeks the foot began to show patchy areas of necrosis. During the ensuing four months these gangrenous patches increased in size and coalesced, and, finally, a thigh amputation was deemed necessary. Pathologic examination of the amputated specimen revealed that the popliteal, posterior tibial, and anterior tibial arteries were completely obstructed by a chronic arteriosclerotic process.

CASE 2.—A white man, aged 63 years, gave a history of intermittent claudication of fifteen months' duration in his left leg. One week before admission he experienced sudden numbness and weakness in the foot.

*Examination.*—The pain was so severe that large doses of analgesics were required. Oscillometric examination revealed absence of pulsation in the lower part of the leg. A pulsation was palpable in the femoral artery, but none could be felt in the popliteal, posterior tibial, or dorsalis pedis arteries. The foot was very cold to the touch, cyanotic, and sweaty. There was extreme pallor of the foot on elevation. There was no ulceration or gangrene. The venous filling time was fifty seconds. A diagnosis of acute thrombosis of an arteriosclerotic popliteal artery was made, and lumbar sympathectomy was performed for the relief of the vasospasm and the intractable pain. Within twenty-four hours the foot became very warm. However, one week after operation the second and third toes began to turn dark and soon became completely gangrenous. Later, a large patch of painful, ischemic necrosis appeared on the dorsum of the foot. The rest of the foot remained warm, but the painful gangrenous parts failed to demarcate, and, two months after the sympathectomy, it was necessary to perform a low thigh amputation. Pathologic examination of the amputated specimen showed that the terminal portion of the femoral and the popliteal arteries was involved by a severe arteriosclerotic process and occluded by an organizing thrombus.

CASE 3.—A 63-year-old white man gave a history that twelve months previously he began to experience burning pain in his right foot; this was accompanied by sensations of coldness and numbness, and by paresthesias. Intermittent claudication was also present. During the preceding year the pain in the foot had progressed to the point where it was intolerable.

*Examination.*—There was extreme pallor of the foot on elevation, with rubor on dependency. Oscillometric examination revealed no pulsation in the lower part of the leg. No pulsation was palpable in the femoral, posterior tibial, dorsalis pedis, or popliteal arteries. The venous filling time was sixty seconds. There was marked atrophy of the skin and subcutaneous tissues of the foot and toes. Neither ulceration nor gangrene was present.

Lumbar sympathectomy was done in an attempt to relieve the intense pain. Within twenty-four hours the foot became very warm to the touch, but the pain was not relieved. One week later an ulcer suddenly appeared on the dorsum of the fifth toe. It refused to heal and became gangrenous. The entire toe then became gangrenous, and the gangrene extended into the foot. During the following four months several patches of gangrene appeared on the dorsum of the foot, and two



large areas of gangrene developed on the inner side of the lower and medial portions of the leg. A thigh amputation was performed. Pathologic examination of the amputated specimen showed total obliteration of the femoral and popliteal arteries by a chronic arteriosclerotic process.

#### DISCUSSION

It is quite evident that one cannot rely too much on surface temperature studies in evaluating the nutritive efficiency of the circulation through an arteriosclerotic foot. In Cases 2 and 3 the skin temperatures of the sympathectomized feet and lower portions of the legs rose to levels in excess of 30° C. as a result of surgically induced relaxation of the distal arteriolar beds, but they became gangrenous after sympathectomy, and probably as a direct result thereof.

Therefore, in evaluating the vascular efficiency of an arteriosclerotic extremity, the important consideration is whether any therapeutic attempt to produce peripheral vasodilatation will actually increase the flow of blood through the capillary bed, where it can do some good; and the important factor in such an evaluation revolves about the presence or absence of an adequate collateral circulation. Unless an effective collateral circulation is present, blood will not reach the foot in sufficient quantity to more than compensate for that which is shunted away from the capillary bed as a result of the therapeutically induced relaxation of the arteriovenous anastomoses. Under such circumstances, vasodilating methods may do more harm than good.

The value of instrumental procedures in gauging collateral circulation is limited. An effective collateral circulation may be present even when arterial pulsations, as measured by the oscillogram, are absent. A *rapid* rise in the distal skin temperatures to vasodilatation levels of at least 30° C. after a diagnostically induced relaxation of the peripheral arterioles, with concomitant fading of cyanosis, indicates the presence of an adequate collateral circulation. However, failure to obtain such a favorable response may be merely the result of an unusually persistent degree of vasoconstrictor tone or of faulty technique. On the other hand, if the arteriovenous anastomoses are flexible, a slow rise in the distal skin temperatures may follow sympathectomy in the presence of a greatly impaired collateral circulation.

Therefore, it may become necessary to base one's evaluation chiefly on clinical observations. A combination of constant, severe pain in the foot, extreme pallor of the foot on elevation, cyanosis and rubor on dependency, atrophy of the skin and its appendages, thinning, with a loss of elasticity, of subcutaneous tissue, significantly delayed filling of the emptied dorsal venous arch, and an increase in pain and cyanosis on immersing the foot in warm water can be accepted as evidence of advanced involvement of the collateral circulation by the obliterating

process. Absence of this combination indicates that there is an open and healthy circulation, and only in such cases should lumbar sympathectomy be performed.

Even if it is otherwise indicated, sympathetic denervation of an arteriosclerotic leg and foot should be avoided when symptoms or an exacerbation of symptoms are of recent origin. In such instances the diminution in peripheral blood flow and the increase in blood coagulability which follow operation may accelerate the spread of a fresh thrombotic process. When one is in doubt as to the activity of a thrombotic process, it is best to postpone operation for a period of six months, during which time the patient can be treated conservatively.

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## ANGINA PECTORIS

### SIGNIFICANT ELECTROCARDIOGRAPHIC CHANGES FOLLOWING EXERCISE

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THE diagnosis of angina pectoris today rests essentially upon the patient's symptoms and upon the interpretation of these symptoms by the physician. Frequently the diagnosis is difficult to establish because the symptoms are atypical and bizarre and because indefinite pain in the chest occurs in cardiac diseases other than angina pectoris. The establishment of objective evidence would be of inestimable value in consideration of the grave prognosis in angina pectoris, of its increasing frequency, especially in the earlier decades of life, and, in approximately 25 per cent of the cases, of the negative results of physical, roentgenologic, and routine electrocardiographic examination.<sup>1</sup>

According to the present concept, angina pectoris is caused by transient coronary insufficiency, i.e., a relative disproportion at a given moment between the coronary blood flow and the work of the heart. Coronary disease is, of course, the predominant underlying lesion. But many other conditions, such as aortic valvular disease, thyrotoxicosis, anemia, and paroxysmal arrhythmia, may also unmask latent coronary disease and produce angina pectoris.

In the search for objective criteria, electrocardiographic studies have been made during induced attacks of coronary insufficiency. For various reasons (such as small number of patients, inadequate controls, infrequent use of the chest lead), no general agreement has been reached as to the value of the methods used. We have reinvestigated the problem by inducing coronary insufficiency with a standard exercise test and by taking four-lead electrocardiograms during the induced attack.

Various methods have been used to induce coronary insufficiency. Levine, et al.,<sup>2</sup> first suggested adrenalin, but the lack of control over the parenterally injected drug, the unpleasant subjective reaction even in normal persons, and the danger of producing a severe attack militated against its use. Greene and Gilbert<sup>3</sup> first studied the effect of rebreathing on the electrocardiogram in normal persons, and Rothseild and Kissin<sup>4-6</sup> were the first to apply this test to patients with angina pectoris. They noted S-T depression in controls and in cardiac patients with and

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without angina. The degree of deviation was related to the degree of anoxemia. By the same technique, Katz, Hamburger, and Schultz<sup>7</sup> studied normal persons and patients with angina pectoris. In both groups, depression of the S-T segment, as well as flattening and inversion of the T waves, occurred. They concluded that some factor in addition to anoxemia is concerned in the production of anginal pain and that this variable makes it impossible to predict accurately whether or not induced anoxemia will cause pain. They discouraged the use of anoxemia because of its variable results and hazards. Levy, et al.,<sup>8, 9</sup> studied the effects of inhaling a 10 per cent oxygen mixture on a large group of normal persons and seventeen patients with definite angina, as well as a group of 115 normal persons and 147 patients with suspected or manifest cardiac disease caused by coronary sclerosis or hypertension. As a result of this study they set up definite criteria for abnormal responses. A few of the patients in the latter group had vasovagal reactions, convulsive seizures, and mental confusion during the test; however, none of these reactions was serious. Positive tests were obtained in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks. Because of the disadvantages previously mentioned, as well as the danger of pulmonary edema, the necessity of insuring accurate concentrations of oxygen, and the elaborate equipment required, the use of this method of producing cardiac anoxemia and angina pectoris will be limited.

For many years, transient electrocardiographic changes have been recorded during spontaneous attacks of angina; the most common are S-T deviation and T-wave changes. The electrocardiographic changes which we have observed during spontaneous and induced attacks of angina are like those of Shapiro and Smyth<sup>10</sup> and Wood and Wolferth.<sup>11</sup>

Wood and Wolferth<sup>11</sup> made standard three-lead electrocardiograms before and after exercise in a study of 162 controls, including cardiac patients without angina, patients with noncardiac pain, and twenty-four patients with angina. None of the controls showed S-T displacement or inversion of the T wave, but one-half of the patients with angina developed these changes after exercise. Chest leads were not employed. Missal<sup>12</sup> reported that in forty normal persons no S-T displacement of more than 1.0 mm. and no reversal of the T wave from its original direction took place after exercise. In forty cases of angina his significant observations were: depression of the S-T segment, inversion of T waves, and temporary disappearance of the Q wave in the chest lead. Lead IV was used in only three cases. Siegel and Feil<sup>13</sup> reported eleven cases of transient anginal attacks, some spontaneous and some precipitated by exercise, in eight of which inversion of the T wave and/or depression of the S-T segment occurred. These changes disappeared after cessation of the pain. Electrocardiograms which were taken during the pains of labor and renal colic revealed no T-wave or S-T changes.

Katz and Landt<sup>14</sup> studied the four-lead electrocardiogram after exercise in twenty cases of angina pectoris; they mentioned no controls. In the standard three leads they noted a shift in axis, changes in T waves opposite to the direction of the QRS, and S-T displacement. In the chest lead they found S-T elevation and T-wave changes. Riseman, et al.,<sup>15</sup> in a recent article, which included a comprehensive review of the literature, reported that they studied twenty patients with angina pectoris (no controls) by taking continuous electrocardiograms and recording only one lead a day before, during, and after exercise over the two-step stairs to the point of pain. S-T deviation was the most common change; nineteen of seventy-six leads showed a change of 1.5 to 3.0 millivolts. Since most of these changes occurred in the chest lead, they studied this lead alone in fifteen controls and fifteen anginal patients after twenty complete trips over the two-step stairs. Only two of the anginal patients experienced pain. In the control group no S-T deviation greater than 1.0 mm. occurred, and the T wave decreased from 2 to 7 mm. in thirteen instances. In eleven of the patients with angina pectoris, deviation of the S-T segment of 1 to 2 mm. was noted, and, in two, of more than 2 mm. The T wave decreased 2 to 7 mm. in four patients and increased 2 to 4 mm. in five patients.

Evans and Bourne<sup>16</sup> took four-lead electrocardiograms on ten controls and twenty patients with angina pectoris whom they submitted to both the anoxemia and the exercise tests. No S-T segment changes or T-wave inversion was noted in the controls, but minor changes occurred in the T-wave voltage. Eleven of the patients with angina showed no changes, and nine showed some changes after anoxemia or exercise. After exercise, diphasic or inverted T waves and variations in the S-T segment, from slight to 2.0 mm., were noted. These authors concluded that the exercise test apparently results in significant changes as often as, and probably more often than, the anoxemia test, and that it is much more easily performed.

Missal<sup>12</sup> stated that electrocardiograms of healthy athletes taken after marathon running show no S-T changes of more than 1.0 mm. Cooper, O'Sullivan, and Hughes<sup>17</sup> obtained electrocardiograms on athletes after strenuous rowing. The electrocardiograms illustrated in their article showed no significant S-T segment or T-wave changes, according to our criteria.

#### PROCEDURE

In our study the exercise test described by Master and Oppenheimer<sup>18</sup> was used. A control electrocardiogram was taken with the patient in the recumbent position. Then, with the electrodes still in place, he was exercised on the stairs (at room temperature) until a typical attack of pain occurred, or, lacking that, until he was tired or dyspneic. Immediately after the exercise he was again placed in the recumbent position and a second electrocardiogram was recorded. Leads IV, I, II, and III were taken in that order. In some cases the pain had ceased after the first

lead or two had been taken; in others it persisted during the entire recording. On an average, three minutes were required to take the electrocardiograms. In some instances the exercise was stopped at the first sign of angina, and, in others, it was continued until the attack was of the severity usually experienced by the patient. In no instance was the induced pain more severe than that experienced by the patient as an everyday occurrence. In some cases of known angina the pain which causes intermittent claudication prevented development of the characteristic sub-sternal pain. No attempt was made to exercise these patients in a different manner. They were allowed to select their own pace and were urged to keep to it without slowing down or "resting." The number of round trips on the two-step stairs varied from eight to fifty; the average was about twenty (depending upon the amount of exercise necessary to produce pain). The controls were exercised at a much faster pace, but also to the point of dyspnea; the average number of round trips was twenty-five. The exercise test was performed without incident. No patient had pain that could not easily be stopped by rest and nitroglycerin. During the entire procedure a physician was in attendance, and notations on the number of trips and on the quality and quantity of pain were made.

#### ANALYSIS OF 100 CONTROL SUBJECTS AFTER EXERCISE

In Table I the control group is classified according to age, sex, and whether the electrocardiogram was normal or abnormal before exercise (called control electrocardiograms). Of the 100 subjects, fifty-six were males and forty-four were females; fifty-nine were over 40 years of age and thirty-six were over 50. There were seventy-two normal and twenty-eight abnormal control electrocardiograms.

TABLE I

CORRELATION OF AGE, SEX, AND NORMAL OR ABNORMAL CONTROL ELECTROCARDIOGRAM IN 100 CONTROL SUBJECTS

| AGE   | MALE                  |                         | FEMALE                |                         |
|-------|-----------------------|-------------------------|-----------------------|-------------------------|
|       | NORMAL<br>CONTROL EKG | ABNORMAL<br>CONTROL EKG | NORMAL<br>CONTROL EKG | ABNORMAL<br>CONTROL EKG |
| 11-20 | 0                     | 0                       | 1                     | 1                       |
| 21-30 | 5                     | 1                       | 8                     | 3                       |
| 31-40 | 11                    | 3                       | 4                     | 4                       |
| 41-50 | 10                    | 1                       | 5                     | 7                       |
| 51-60 | 14                    | 5                       | 4                     | 2                       |
| 61-70 | 4                     | 0                       | 4                     | 0                       |
| 71-80 | 1                     | 1                       | 1                     | 0                       |
| Total | 45                    | 11                      | 27                    | 17                      |

The S-T segment changes were analyzed in each lead. After exercise, no subject developed or exceeded an S-T deviation of 1.0 mm. in Lead I, 1.5 mm. in Lead II, 1.5 mm. in Lead III, or 2.0 mm. in Lead IV. There were, however, many minor segment changes that did not approach those previously mentioned. In Lead I, twenty-seven of these did not exceed 0.5 mm.; in Lead II, twenty-four did not exceed 1.0 mm.; in Lead III, four did not exceed 1.0 mm.; in Lead IV, seventeen did not exceed 1.0 mm., and two showed an S-T deviation of 1.5 mm. There were only six

instances of S-T elevation: four in Lead III not exceeding 1.0 mm., and two in Lead IV not exceeding 1.5 mm.

Many T-wave changes occurred in this group after exercise. Because of the variability of  $T_{3s}$ , this lead was ignored. No persons with an upright  $T_1$ ,  $T_2$ , or  $T_4$  had diphasic or inverted T waves after exercise. Occasionally diphasic or inverted T waves became upright. The responses in voltage were variable; an increase or decrease in the height of the T waves was common. In the limb leads these changes usually did not exceed 2.0 mm., and, in the chest lead, 3.0 mm.; however, changes up to 4 mm. occurred in both. In five instances a previously inverted  $T_4$  became upright after exercise.

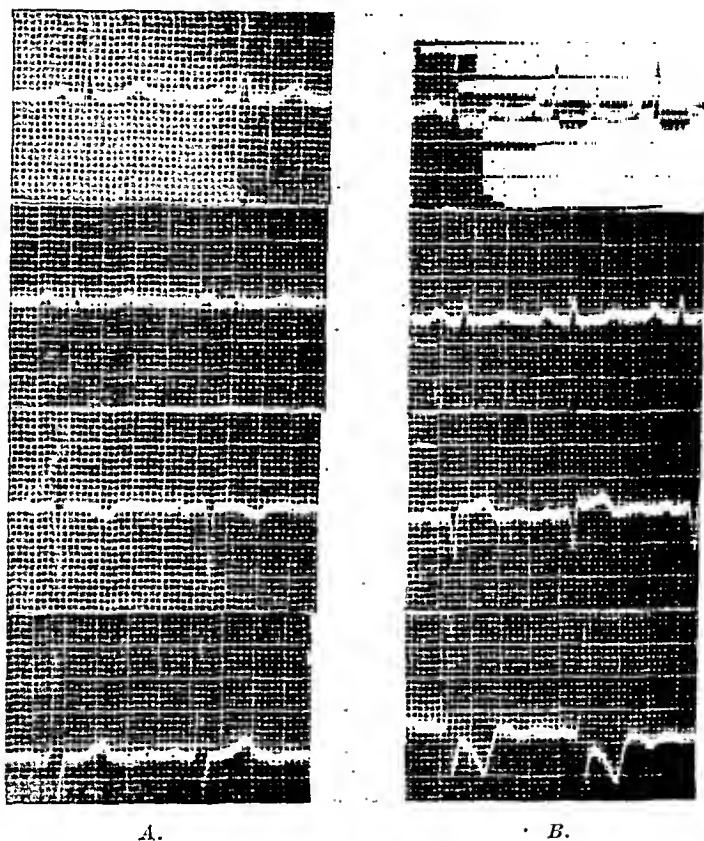


Fig. 1.—Electrocardiogram (A) before and (B) after exercise. Woman (U 51950), aged 54. Lower sternal pain with cholecystitis was considered in diagnosis. Note significant changes with exercise. S- $T_1$  has characteristic contour and depth.

No changes in rhythm were noted, with the exception of occasional extrasystoles. Only slight axis changes and no marked P-wave variations occurred. The P-R conduction time, as well as the duration of QRS, remained within normal limits except in one case, in which a QRS of 0.10 increased to 0.12 second. The average rate increase was approximately 23 per minute.

From our study of these 100 control subjects we concluded that the abnormal electrocardiographic response to exercise consists of an S-T depression or elevation of 1.0 mm. or more in Lead I, of 1.5 mm. or

more in Lead II, of 1.5 mm. or more in Lead III, and of 2.0 mm. or more in Lead IV; or consists of a change from an upright to a diphasic or inverted  $T_1$ ,  $T_2$ , or  $T_4$ . If any one of these changes is present, the curve is considered abnormal.

#### ANALYSIS OF THE RESPONSE OF SIXTY-SIX PATIENTS WITH ANGINA PECTORIS TO EXERCISE

Of the sixty-six patients with angina pectoris, fifty-three were males and thirteen were females, a ratio of 4:1. Fifty of these patients were over 50 years of age; twenty-five, or 38 per cent, had normal control (pre-exercise), four-lead electrocardiograms. In forty-five cases the typical pain of angina pectoris developed during the exercise test; pain was not reproduced in twenty-one. In two instances both angina and bundle branch block developed. Since the presence of bundle branch block interferes with the detailed interpretation of S-T segment and T-wave changes, these two cases will be considered separately.

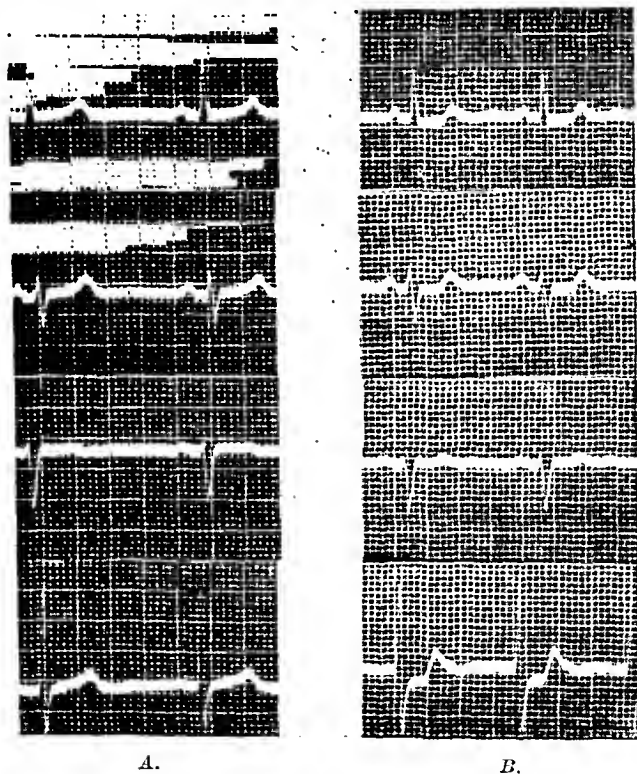


Fig. 2.—Electrocardiogram (A) before and (B) after exercise. Man (U 52773), aged 68. Atypical chest pain did not permit a definite clinical diagnosis of angina pectoris. Death followed six months later from coronary occlusion.

The remaining sixty-four patients were divided into those who developed pain (forty-three) and those who did not develop pain (twenty-one) during the exercise test. Table II shows the incidence and magnitude of the S-T segment changes in the various leads and their correlation with the reproduction or nonreproduction of angina. There were



136 instances of S-T depression, and, in forty-nine of these, it reached a significant level (e.g., what was considered abnormal in comparison with the controls). There were only sixteen instances of S-T elevation, and in only six was it significant.

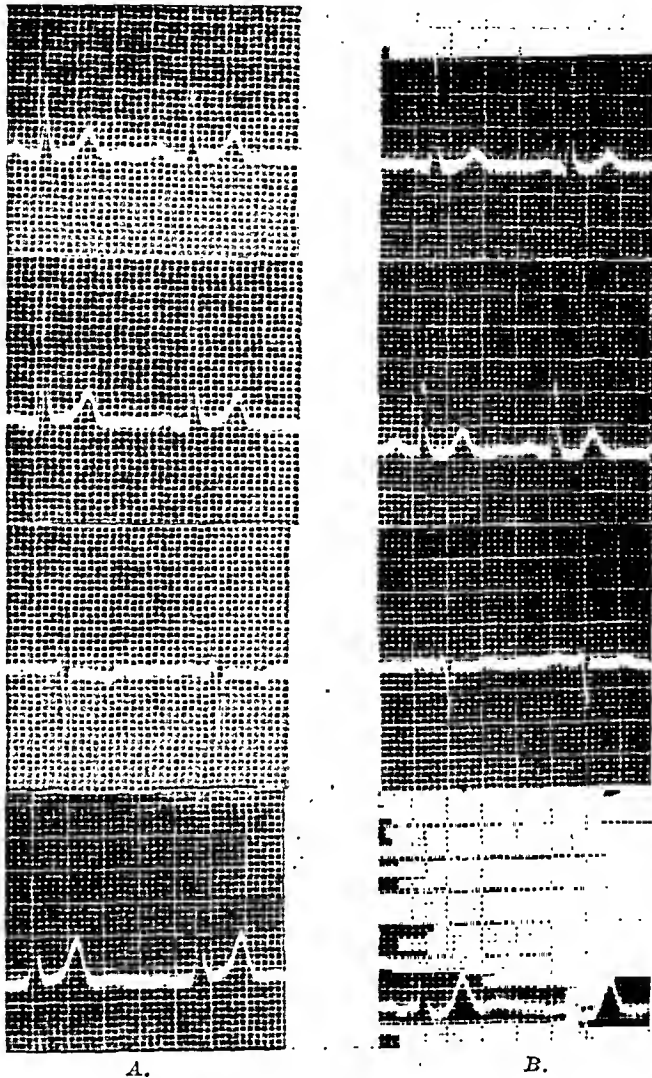


Fig. 3A and B.—Electrocardiogram (A) before and (B) after mild exercise. Man (U 19319), aged 59. Changes after mild exercise and mild pain were not significant.

The distribution of significant S-T segment and T-wave changes in the various leads is shown in Table III. Of the total of fifty-five significant S-T changes, forty-nine, or 89 per cent, were found in cases in which pain was produced by the exercise test, whereas six, or 11 per cent, occurred in cases in which the test failed to reproduce angina; twenty-three, or 41 per cent, occurred in Lead IV. Of the total of twenty-six significant T-wave changes, twenty-one, or 80 per cent, were found in the patients who experienced pain on exercise, whereas six, or 20 per cent, occurred in patients who did not have pain with exercise; seven, or 27 per cent, occurred in Lead IV. Of the total of eighty-

one significant S-T segment and T-wave changes, seventy, or 86 per cent, occurred when pain was reproduced, and eleven, or 14 per cent, occurred when pain was not elicited.

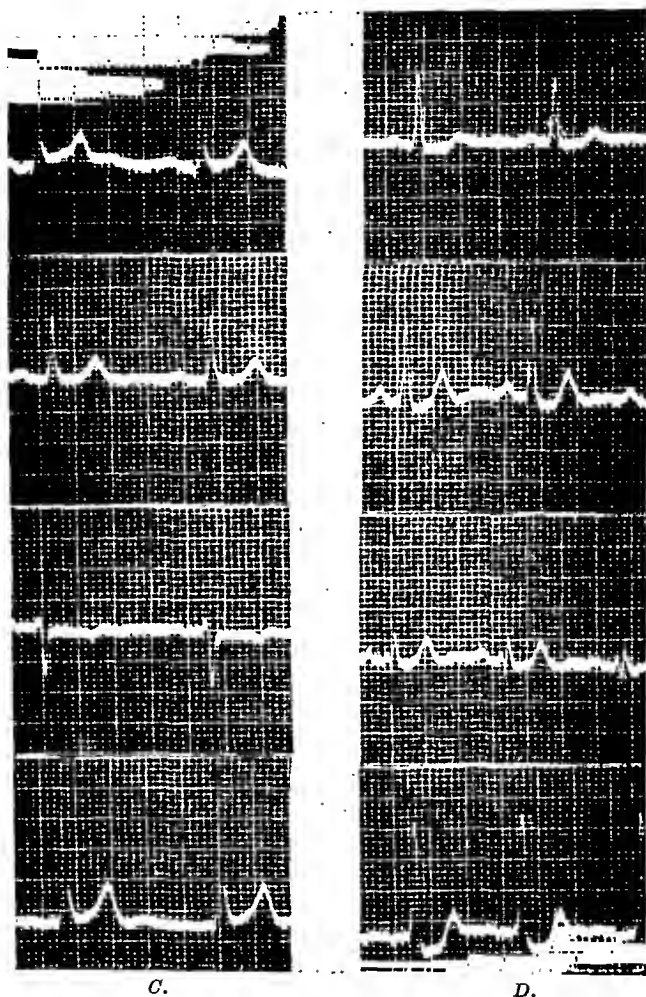


Fig. 3C and D.—Electrocardiogram (C) before and (D) after severe exercise. Man (U 19319), aged 59. Changes after severe exercise and pain of usual severity were considered significant.

Table IV gives the number of cases of angina pectoris (including the two patients with bundle branch block) in which significant four-lead electrocardiographic abnormalities developed after exercise; it shows whether or not the S-T segment and T-wave changes occurred separately or in combination; and it correlates these changes with the reproduction or nonreproduction of pain. It reveals the importance of eliciting an attack of typical chest pain during the exercise test. Electrocardiograms characteristic of coronary insufficiency were obtained in two-thirds of the forty-five cases in which pain was reproduced, and in only one-third of the twenty-one cases in which pain was not reproduced on exercise.

TABLE II

S-T SEGMENT CHANGES OF THE STANDARD FOUR-LEAD ELECTROCARDIOGRAM IN SIXTY-FOUR PATIENTS WITH ANGINA PECTORIS FOLLOWING EXERCISE; CORRELATION WITH REPRODUCTION (P) OR NONREPRODUCTION (NP) OF TYPICAL ANGINAL PAIN

| S-T SEGMENT DEVIATION | MM. | LEAD I |    | LEAD II |    | LEAD III |    | LEAD IV |    |
|-----------------------|-----|--------|----|---------|----|----------|----|---------|----|
|                       |     | P      | NP | P       | NP | P        | NP | P       | NP |
| No change             | 0.0 | 13     | 12 | 15      | 14 | 16       | 18 | 5       | 11 |
| Depression            | 0.5 | 14     | 4  | 10      | 3  | 13       | 7  | 6       | 7  |
|                       | 1.0 | 11     | 5  | 9       | 4  | 2        | 1  | 3       | 2  |
|                       | 1.5 | 4      | 0  | 5       | 0  | 0        | 0  | 2       | 0  |
|                       | 2.0 | 1      | 0  | 3       | 0  | 0        | 0  | 10      | 1  |
|                       | 2.5 | 0      | 0  | 0       | 0  | 0        | 0  | 6       | 0  |
|                       | 3.0 | 0      | 0  | 0       | 0  | 0        | 0  | 0       | 0  |
|                       | 3.5 | 0      | 0  | 0       | 0  | 0        | 0  | 1       | 0  |
|                       | 4.0 | 0      | 0  | 0       | 0  | 0        | 0  | 1       | 0  |
|                       | 4.5 | 0      | 0  | 0       | 0  | 0        | 0  | 1       | 0  |
| Elevation             | 0.5 | 0      | 0  | 0       | 0  | 5        | 0  | 1       | 0  |
|                       | 1.0 | 0      | 0  | 0       | 0  | 0        | 0  | 2       | 0  |
|                       | 1.5 | 0      | 0  | 0       | 0  | 1        | 0  | 2       | 0  |
|                       | 2.0 | 0      | 0  | 1       | 0  | 1        | 0  | 2       | 0  |
|                       | 2.5 | 0      | 0  | 0       | 0  | 0        | 0  | 0       | 0  |
|                       | 3.0 | 0      | 0  | 0       | 0  | 0        | 0  | 0       | 0  |
|                       | 3.5 | 0      | 0  | 0       | 0  | 0        | 0  | 1       | 0  |

TABLE III

DISTRIBUTION OF SIGNIFICANT CHANGES IN THE VARIOUS LEADS IN ANGINAL PATIENTS FOLLOWING EXERCISE; CORRELATION WITH REPRODUCTION (P) OR NONREPRODUCTION (NP) OF PAIN

| LEAD  | SIGNIFICANT S-T SEGMENT CHANGES |    | SIGNIFICANT T-WAVE CHANGES |    |
|-------|---------------------------------|----|----------------------------|----|
|       | P                               | NP | P                          | NP |
| I     | 16                              | 5  | 11                         | 1  |
| II    | 9                               | 0  | 6                          | 1  |
| III   | 2                               | 0  |                            |    |
| IV    | 22                              | 1  | 4                          | 3  |
| Total | 49                              | 6  | 21                         | 5  |

TABLE IV

SUMMARY OF THE TYPE AND INCIDENCE OF SIGNIFICANT CHANGES IN THE FOUR-LEAD ELECTROCARDIOGRAM FOLLOWING EXERCISE IN SIXTY-SIX PATIENTS WITH ANGINA PECTORIS (INCLUDING TWO PATIENTS WITH BUNDLE BRANCH BLOCK); CORRELATION WITH REPRODUCTION OR NONREPRODUCTION OF PAIN

|         | NO. OF PATIENTS | SIGNIFICANT CHANGES |                |                                      |                     |       |                  |
|---------|-----------------|---------------------|----------------|--------------------------------------|---------------------|-------|------------------|
|         |                 | S-T SEGMENT (ALONE) | T WAVE (ALONE) | S-T SEGMENT AND T WAVE (COMBINATION) | BUNDLE BRANCH BLOCK | TOTAL | PER CENT         |
| Pain    | 45              | 15                  | 1              | 12                                   | 2                   | 30    | 66 $\frac{2}{3}$ |
| No pain | 21              | 2                   | 2              | 3                                    | 0                   | 7     | 33 $\frac{1}{3}$ |
| Total   | 66              | 17                  | 3              | 15                                   | 2                   | 37    | 56               |

Irrespective of the presence or absence of pain during the test, 56 per cent of the total of sixty-six patients had significant electrocardiographic changes after exercise.

TABLE V

RELATIVE IMPORTANCE OF STANDARD AND CHEST LEADS IN THIRTY-SEVEN PATIENTS WITH SIGNIFICANT ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE (INCLUDING TWO PATIENTS WITH BUNDLE BRANCH BLOCK)

| LEADS                                  | SIGNIFICANT CHANGES |          |
|--|---------------------|----------|
|  | NO. OF PATIENTS     | PER CENT |
| Standard leads alone                   | 12                  | 32½      |
| Chest lead alone                       | 8                   | 21½      |
| Standard leads and chest lead combined | 17                  | 46       |

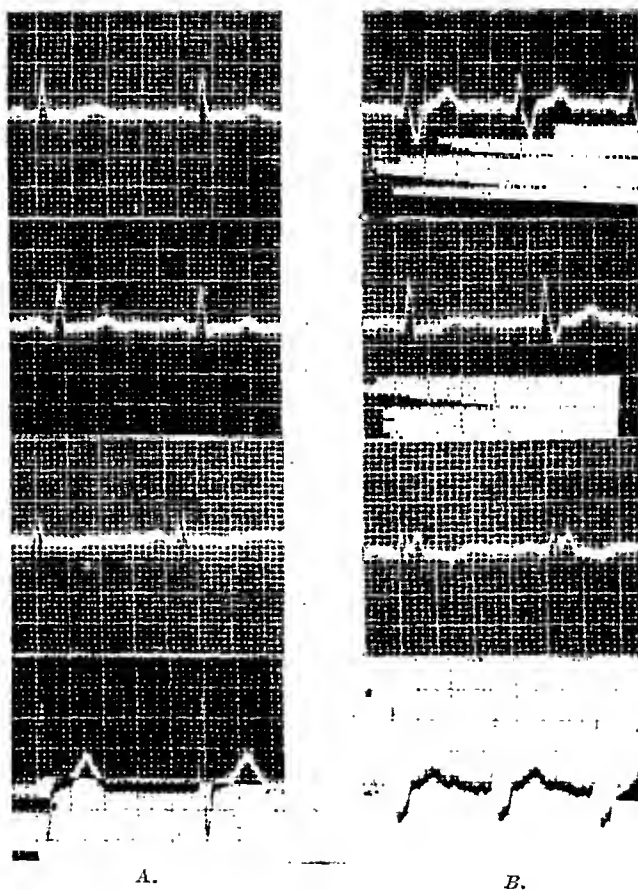


Fig. 4.—Electrocardiogram (A) before and (B) after exercise. Man, aged 45. Note bundle branch block after exercise.

Table V shows the relative importance of the standard leads and the chest lead. The chest lead was abnormal in twenty-five of the thirty-seven patients (67 per cent) with significant electrocardiographic changes; in eight patients (21.5 per cent) it showed the only significant change which was noted in the four-lead electrocardiogram.

Figs. 1 to 7 illustrate typical electrocardiographic changes after exercise.

## DISCUSSION

A study of the control (nonangina) group reveals that in the four-lead electrocardiogram there were seventy-three instances of S-T deviation. In cases of angina, the development of S-T changes alone after exercise cannot be considered important unless they reach a certain magnitude. Of 152 S-T segment changes in the cases of angina pectoris,

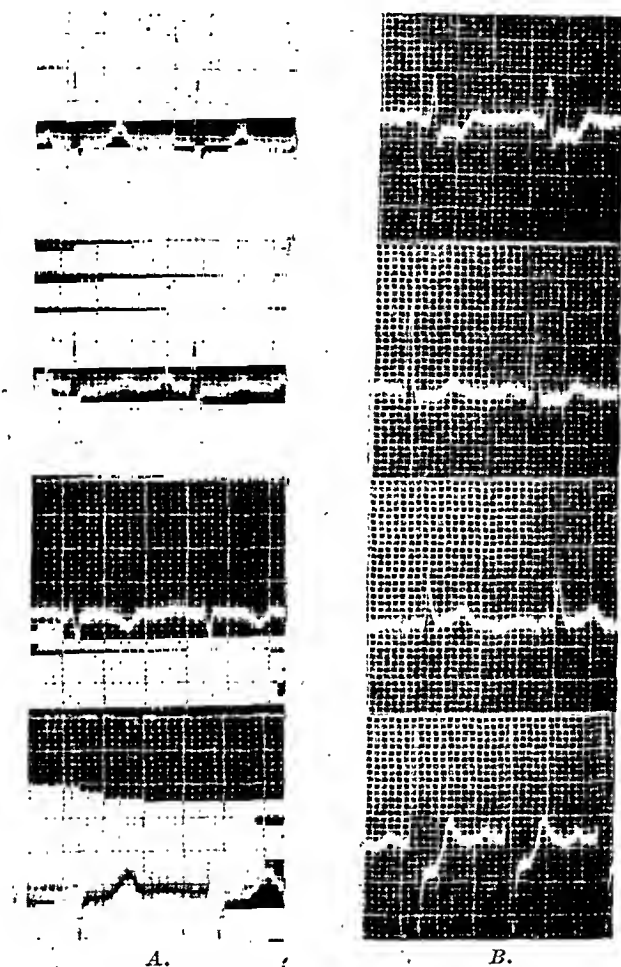


Fig. 5.—Electrocardiogram (A) before and (B) after exercise. Man, aged 60. Note T-wave and S-T segment changes. Pain was produced by exercise.

only fifty-five were significant (elevation or depression). The infrequency of elevation should be noted. Only in rare instances were the changes reciprocal. The contour of the S-T segment was variable; there was either a smooth, rounded type of depression, or a very rapid depression, with flattening of the main portion of the segment, followed by a quick return to the isoelectric line, such as is found in certain types of coronary arterial disease. The latter type of contour, as illustrated in Fig. 1 (S-T<sub>1</sub>, after exercise), is very important. Many of the patients with angina pectoris showed this characteristic change in contour, although the degree of the S-T depression was not abnormal. We did not use this contour change as a criterion for a positive test because it is sub-

ject to individual interpretation, and, unlike the depth of the S-T segment deviation, cannot be measured accurately. However, if this characteristic contour of the S-T segment is found, coronary insufficiency may be present regardless of the depth of the S-T deviation. Future observations will determine the importance of the "significant contour" without significant deviation of the S-T segment.

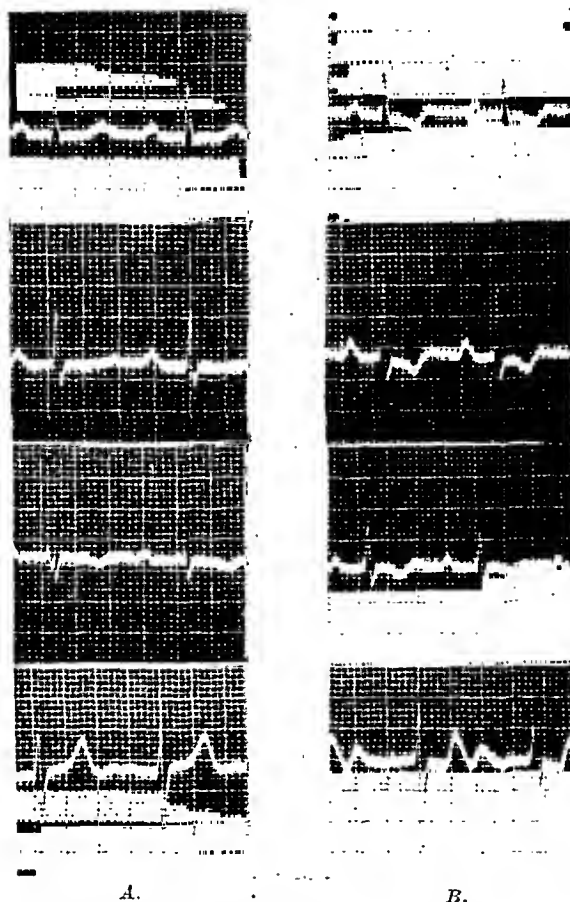


Fig. 6.—Electrocardiogram (A) before and (B) after exercise. Woman (U 54971), aged 60. Angina pectoris with pain was produced on exercise. Note changes in  $T_1$  and  $T_2$ .

The variability of the T-wave changes in the control group was striking. A variation in voltage of the T waves, as well as a change from an inverted T wave to an upright one, was commonly found. The only significant change, however, was the development of an abnormal T wave from one that had previously been normal.

In cases of angina pectoris, careful study of axis deviation, Q waves, and rate changes did not reveal anything significant as compared to the control series. Occasionally a patient showed slight prolongation of the P-R or QRS interval, extrasystoles, or minor P-wave changes after exercise. The significance of these changes was not ascertained.

The electrocardiographic changes after exercise in cases of angina pectoris are not dependent upon the production of pain, as is illustrated in the tables, although the percentage of positive results is much greater if pain is induced. When pain is produced by exercise, objective electrocardiographic evidence is obtained in two-thirds of the cases; when pain is not reproduced by exercise, only one-third of the patients have significant electrocardiographic abnormalities. The importance of the chest lead must be stressed, for eight of the thirty-seven significant changes occurred in Lead IV alone. This explains why we had a much greater number of positive results than previous workers who did not use chest leads. Of course, one should use a combination of limb and chest leads.

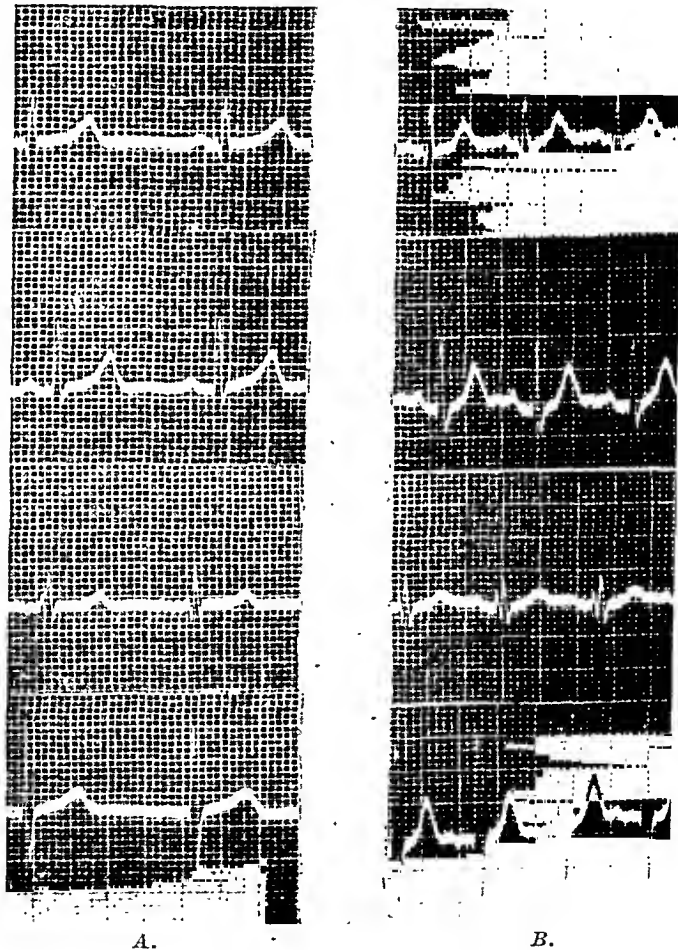


Fig. 7.—Electrocardiogram (A) before and (B) after exercise. Control subject, woman, aged 25. Note S-T segment contour in Lead II as contrasted with the abnormal S-T contour in Fig. 3.

More positive curves might have been obtained if serial tracings had been taken at varying intervals after exercise; if some of the patients had been exercised more strenuously; if patients suffering from arthritis and intermittent claudication had been given a different type of exercise; or, if the characteristic contour of the S-T segment had been added to

the criteria. The criteria that have been established may have to be altered upon further investigation.

Changes caused by exercise offer objective evidence of angina pectoris (coronary insufficiency), but a normal response does *not* rule out the presence of coronary insufficiency.

#### CONCLUSIONS

1. Objective evidence of angina pectoris can be obtained from electrocardiographic changes in two-thirds of all cases if the pain is reproduced by exercise, and in only one-third if the pain is not reproduced by exercise. Significant electrocardiographic changes developed after exercise in 56 per cent of our patients with angina pectoris, irrespective of the absence or presence of pain.

2. In cases of angina pectoris, the significant electrocardiographic changes after exercise are: S-T segment depression or elevation of 1.0 mm. or more in Lead I, of 1.5 mm. or more in Lead II, of 1.5 mm. or more in Lead III, and 2.0 mm. or more in Lead IV; or the conversion of an upright to a diphasic or inverted T wave in Lead I, II, or IV; or the development of bundle branch block. If any one of these changes occurs, the electrocardiogram is considered abnormal.

3. The use of the chest lead increases the number of abnormal curves by approximately 20 per cent.

4. A normal response to exercise does not rule out angina pectoris.

We wish to acknowledge the technical assistance rendered by Miss Ola E. Nagle.

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## THE VASOMOTOR CENTER ESSENTIAL IN MAINTAINING RENAL HYPERTENSION

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IT HAS already been noted that, in the rat<sup>1</sup> and rabbit,<sup>2</sup> destruction of the central nervous system reduces the arterial pressure of animals with renal hypertension to the same level as that of pithed controls. Since pithed animals are notably sensitive to pressor agents such as pitressin, epinephrine, tyramine, and renin,<sup>3</sup> it seemed highly improbable that a peripherally acting vasoconstrictor was present in rodents with renal hypertension. It was more reasonable to assume that the renal pressor hormone acted upon and through the vasomotor control mechanism.

As variation with species must be considered, these observations have now been extended to a carnivore, the dog, and the effect of section of the brain stem above the pons has also been studied. Neither the latter procedure nor section of the spinal cord at C<sub>4</sub> reduced the pressure of dogs with renal hypertension to levels approaching those of controls subjected to the same procedures. Complete destruction of the neuraxis in dogs does abolish the pressure difference between control and markedly hypertensive animals.

### METHODS

Hypertension in dogs was produced by encasing both kidneys in gauze and collodion jackets; in some cases one renal artery was ligated a month or so later. Not all animals became hypertensive, but, within seven to fifteen weeks, most did, and in some this was so severe as to cause retinal separation, extreme irritability, and loss of weight.

Morphine-ether anesthesia was induced before performing the laminectomies, trephinings, and tracheal and carotid cannulations which were necessary for the final experiments. Artificial respiration was started before pithing and maintained thereafter; the blood pressure was recorded from the carotid artery by a mercury manometer. In some instances pithing was performed through a laminectomy, but in most cases through a small parietal trephine opening. Pithing was performed with three heavy wires twisted together, with a heavy solder bead at the tip, and spiralled so that, after insertion and rotation, the medulla and cord were effectively destroyed.

In order to sever the brain stem rostral to the pons, a trephine opening to the right of the vertex was extended with rongeurs down into the temporal bone, and a linear incision in the dura was made. When the other operative procedures were

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complete, and a control level of blood pressure recorded, an open clamp was introduced with one blade on the floor of the skull and the tip of the other near the vault. When this had been inserted as far as possible, the clamp was closed. Subsequent dissection, fixation, and midline section of the brain showed that the crushed tissue included parts of the parietal and temporal lobes, cerebral peduncles, and the brain stem at a level from the middle to the front of the corpora quadrigemina above, and the mammillary bodies, or the tissue within 1 cm. caudal to them, below.

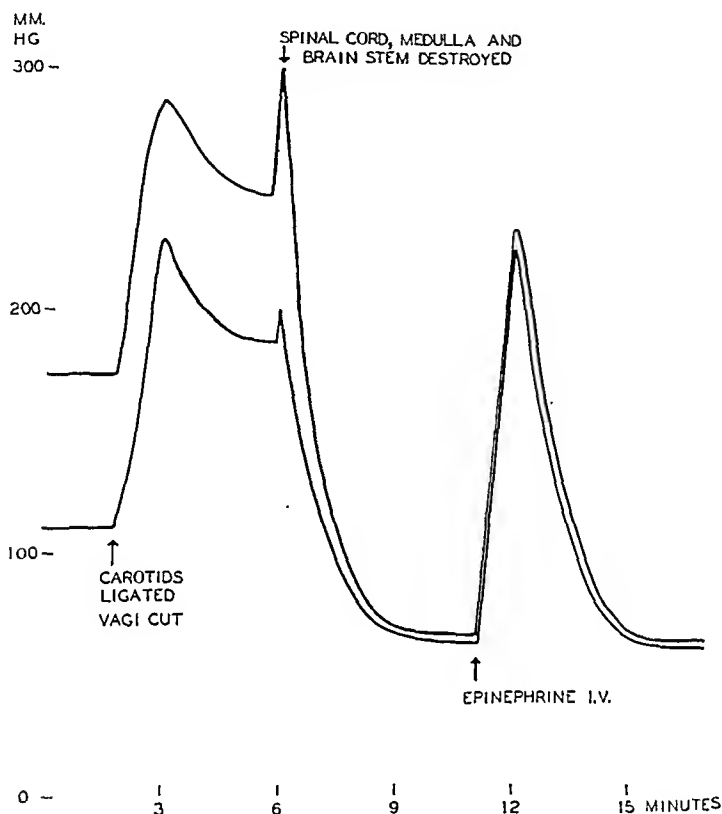


Fig. 1.—This is a composite of the arterial pressure changes in fourteen hypertensive dogs (upper curve) and twelve controls as the moderator nerves were eliminated, the animals pithed, and epinephrine (12 to 15 gamma per kilogram) given intravenously. Artificial respiration throughout.

## RESULTS

In three hypertensive and three control dogs it was noted that only a slight fall in pressure occurred when the cervical cord was cut at  $C_3$  or  $C_4$  under ether anesthesia; the rise in pressure consequent on carotid ligation and vagus section was not strikingly diminished. These facts are of interest, for Root and McAllister<sup>4</sup> have shown that, in dogs which have regained a normal arterial pressure level after cord section, ether anesthesia leads to a profound fall in pressure, and Lim and his co-workers<sup>5-7</sup> have observed that crushing the cervical cord of dogs under chloralose anesthesia causes little fall in pressure and does not prevent a rise on stimulating the central stump of the severed vagus. Pithing the cord below  $C_4$  led to a drop in pressure which was more marked in the hypertensive than in normal animals, but the average level of the

hypertensives after pithing in this way was 102 mm., and that of normals, 81 mm. Hg. This merely confirmed the observations of Glenn and his co-workers,<sup>8, 9</sup> who reported an immediate drop in the pressure of both hypertensive and normal dogs on destroying the cord below C<sub>4</sub>, but with a higher level persisting in the hypertensives.

TABLE I

EFFECT OF LIGATING THE DOG'S COMMON CAROTID ARTERIES AND CUTTING THE VAGI TO ELIMINATE THE MODERATOR NERVES, AND OF COMPLETE PITHING

| NO.                         | ARTERIAL PRESSURE (MM. HG) |     |     |    |     | RENAL HYPERTENSIVES |     |     |      |      |
|-----------------------------|----------------------------|-----|-----|----|-----|---------------------|-----|-----|------|------|
|                             | CONTROLS                   |     |     |    |     | A                   | B   | C   | D    | E    |
| 1                           | 115                        | 205 | 202 | 70 | 250 | 190                 |     |     | 88   |      |
| 2                           | 110                        | 265 | 200 | 70 | 215 | 145                 |     |     | 90   | 250  |
| 3                           | 105                        | 210 | 175 | 65 | 240 | 155                 | 240 | 225 | 50   |      |
| 4                           | 85                         | 220 | 140 | 80 | 210 | 225                 | 340 | 275 | 80   | 270  |
| 5                           | 115                        | 235 | 170 | 60 | 220 | 165                 | 300 | 280 | 70   | 270  |
| 6                           | 90                         | 270 | 200 | 60 | 210 | 145                 | 250 | 190 | 50   | 190  |
| 7                           | 130                        | 245 | 215 | 60 | 230 | 147                 | 240 | 230 | 65   | 230  |
| 8                           | 125                        | 270 | 210 | 50 | 260 | 200                 | 320 | 255 | 60   | 200  |
| 9                           | 118                        | 225 | 210 | 55 | 195 | 200                 | 295 | 260 | 50   | 195  |
| 10                          | 125                        | 200 | 175 | 80 | 225 | 212                 | 340 | 250 | 80   | 260  |
| 11                          | 115                        | 185 | 170 | 60 | 230 | 175                 | 245 | 220 | 50   | 230  |
| 12                          | 100                        | 220 | 150 | 50 | 210 | 175                 | 275 | 260 | 60   | 240  |
| 13                          |                            |     |     |    |     | 160                 | 305 | 295 | 67   | 210  |
| 14                          |                            |     |     |    |     | 145                 | 285 | 245 | 63   | 260  |
| Av.                         | 110                        | 229 | 185 | 63 | 226 | 174                 | 286 | 248 | 66   | 234  |
| % difference, hypertensives |                            |     |     |    |     | +58                 | +29 | +34 | +4.5 | +3.5 |

Column A, initial mean carotid pressure; B, peak reached on cutting the vagi; C, stabilized level after vagal section and prior to pithing; D, level established after pithing; E, peak of the response to epinephrine in the pithed dog. The hypertensive dogs had chronic perinephritis (I. H. Page's method).

It was noted, however, that, when the entire neuraxis was destroyed, the pressure of fourteen hypertensive dogs fell to 50 to 90 mm. (average, 66 mm.; and that of twelve control animals to 50 to 80 mm. (average, 63 mm.). The rise on giving epinephrine reached 234 mm., on the average, in the hypertensive pithed animals, and 226 in the pithed controls. It thus became evident that, although dogs pithed under ether are responsive to a peripheral vasoconstrictor such as epinephrine, they show no evidence of a circulating vasoconstrictor substance, even when renal hypertension is marked at the time of pithing.

Cutting off the flow of impulses from the carotid sinus and great vessels by carotid ligation and vagal section caused a marked rise in pressure in normal dogs, and also in the hypertensive dogs. The peak pressure reached in the hypertensives was 112 mm. (65 per cent) above the control level, and the pressure became stabilized 74 mm. (42 per cent) above the control value. In controls the peak was 119 mm. (104 per

cent) above the control; the stabilized level was up 75 mm. (+68 per cent) from the control figure. It was from these stable levels that the pressures fell to 66 and 63 mm. on pithing (Fig. 1 and Table I).

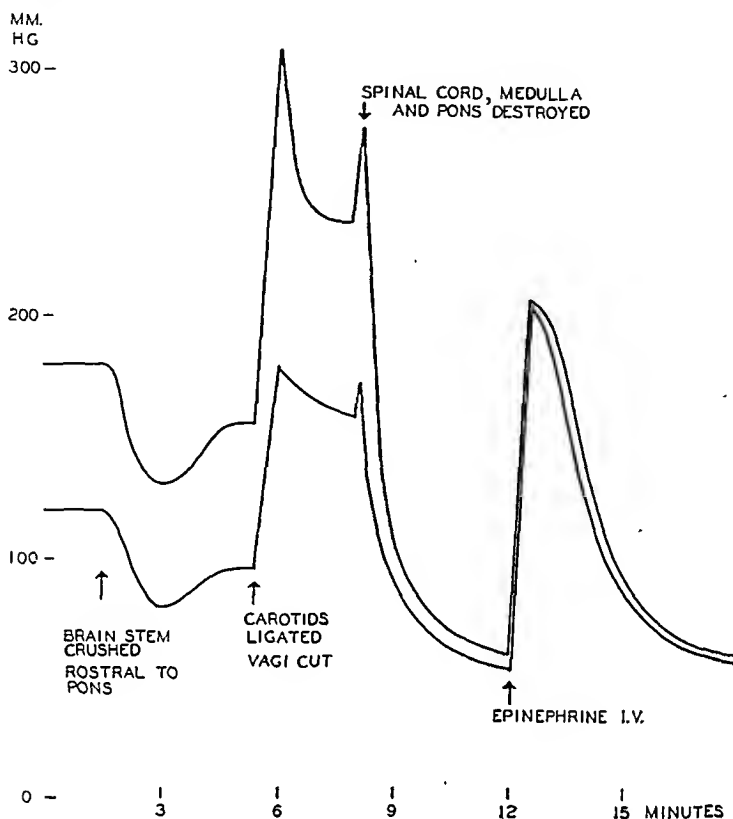


Fig. 2.—This is a composite of the arterial pressure changes in five hypertensive, but only two control, dogs (lower curve), which were subjected to destruction of the brain stem rostral to the pons, then to elimination of the moderator nerves, pithing, and intravenous injection of epinephrine. The brain stem was crushed with a hemo-stat; the line of crushing passed through the anterior half of the corpora quadrigemina, and through, or just caudal to, the mammillary bodies.

TABLE II

EFFECT OF CRUSHING THE DOG'S BRAIN STEM AT THE LEVEL OF THE CORPORA QUADRIGEMINA, THEN LIGATING THE CAROTIDS AND CUTTING THE VAGI, AND, FINALLY, COMPLETE PITHING

| DOGS                 | ARTERIAL PRESSURES (MM. HG) |     |     |     |     |    |     |
|----------------------|-----------------------------|-----|-----|-----|-----|----|-----|
|                      | A                           | B   | C   | D   | E   | F  | G   |
| <i>Controls</i>      |                             |     |     |     |     |    |     |
| C 1                  | 125                         | 65  | 87  | 170 | 170 | 60 | 230 |
| C 2                  | 115                         | 95  | 105 | 185 | 150 | 50 | 180 |
| <i>Hypertensives</i> |                             |     |     |     |     |    |     |
| H 1                  | 200                         | 100 | 115 | 200 | 180 | 50 | 180 |
| H 2                  | 150                         | 92  | 130 | 300 | 270 | 60 | 190 |
| H 3                  | 160                         | 130 | 195 | 270 | 255 | 65 | 190 |
| H 4                  | 182                         | 160 | 160 | 310 | 195 | 60 | 200 |
| H 5                  | 220                         | 180 | 207 | 360 | 285 | 80 | 260 |

Column A, initial pressure level; B, lowest level after crushing the brain stem; C, stable level after crushing; D, peak reached after vagal section; E, stable level before pithing; F, level established after pithing; G, peak of the response to epinephrine.

Five hypertensive dogs, but only two controls, were used to study the effect of destroying the brain stem rostral to the pons. The extensive

trephining and the crushing of the brain stem led to considerable blood loss, so that it was not surprising that, in response to epinephrine, the blood pressure after complete pithing rose only to 205 mm. in controls, and to 207 in the dogs which had been hypertensive. Nor was it surprising that the rise on cutting the moderator nerves and tying the carotids reached only 178 mm., and leveled off at 160 mm. in the controls, instead of reaching 229, as it did in controls with brain stems intact. However, in the hypertensive dogs the rise on vagal section and carotid ligation reached 308 mm., on the average, when the brain stem had been cut, which was 22 mm. higher than it went in those with intact brain stems. Although the crushing of the brain stem caused a transient fall, with partial recovery, it is obvious that structures rostral to the pons are not needed for the maintenance of renal hypertension or for the pressor response on cutting off the inflow from the moderator nerves (Fig. 2 and Table II).

#### DISCUSSION

From these observations it is apparent that the dog, like the rat and rabbit,<sup>1, 2</sup> does not have any demonstrable peripherally acting vasoconstrictor substance at a time when it is markedly hypertensive as a result of renal manipulation. In the rabbit it was proved that the fall of blood pressure on pithing was not due in any significant degree to shock, with low venous pressure. The venous pressure fell very little on pithing; raising it far above the control level by intravenous infusion did not abolish the hypotension in pithed rabbits, whether controls or renal hypertensives, and on giving epinephrine a marked rise in arterial pressure preceded any change in venous pressure. Since pithed carnivora are known to be exquisitely responsive to injections of renin<sup>3</sup> and other pressor substances, it seems certain that, if such substances were present in renal hypertension, pithing would accentuate the pressure difference between these animals and controls. Instead, it abolished the pressure difference.

It is realized that neither sympathectomy<sup>10-12</sup> nor destruction of the cord below C<sub>4</sub><sup>8, 9</sup> abolishes the difference between normal and renal hypertensive dogs, although the latter procedure causes in both groups a striking transient fall, with return to the original levels in a few days. Just how the vasomotor center regains its control after such denervations is not known, but it has been repeatedly shown that hypothalamic stimulation<sup>6</sup> or stimulation of the central stump of the vagus<sup>5-7, 13</sup> causes a rise in pressure in dogs after severing all the structures in the neck save the carotid arteries and jugular veins. Humoral mechanisms, i.e., one involving the postpituitary<sup>5-7, 13</sup> and one involving the superior cervical sympathetic ganglia,<sup>13</sup> are available and may participate in vasomotor regulation after peripheral denervation. Such mechanisms presumably

become more effective in chronic experiments, so that acute, total destruction of the neuraxis must be used to test whether or not the vasomotor center participates in renal hypertension. Observations based on partial chronic denervation<sup>8-12</sup> led to the belief that the renal pressor hormone must act peripherally. This no longer seems tenable.

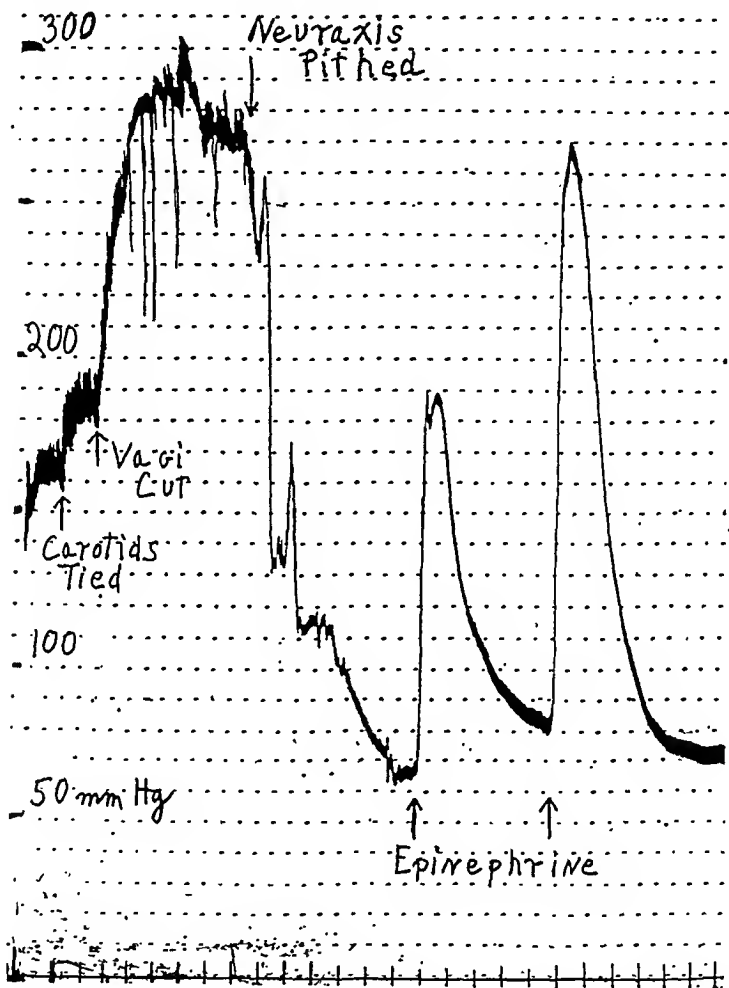


Fig. 3.—Arterial pressure curve, Dog 5, renal hypertensive group, Table I.

There is evidence that in man, also, renal hypertension is not due to peripheral action of a renal pressor substance. In the limbs, flow has been measured after maximal inhibition of vasomotor tone by warming the body, and by nerve block. This has revealed rates of flow equal to, or greater than, the flow in normal limbs under similar conditions.<sup>14-17</sup> One observer has found that the blood flow in the forearm under basal conditions is higher in hypertensives than in normals.<sup>18</sup> The most convincing proof was given by Pickering,<sup>16</sup> who studied flow in the vasodilated forearm of the same subjects during and after recovery from the hypertension of acute nephritis. Here, chronic trophic changes in vessels were eliminated, and there was no question that the hypertension was of purely renal origin. In every case the flow was higher when the

subject was hypertensive; the increase in volume per minute was proportional to the increase in pressure at the time of observation. The idea that there is a peripherally acting vasoconstrictor substance seems thus to have been completely disproved in the renal hypertension of man, as it has in the dog, rabbit, and rat.

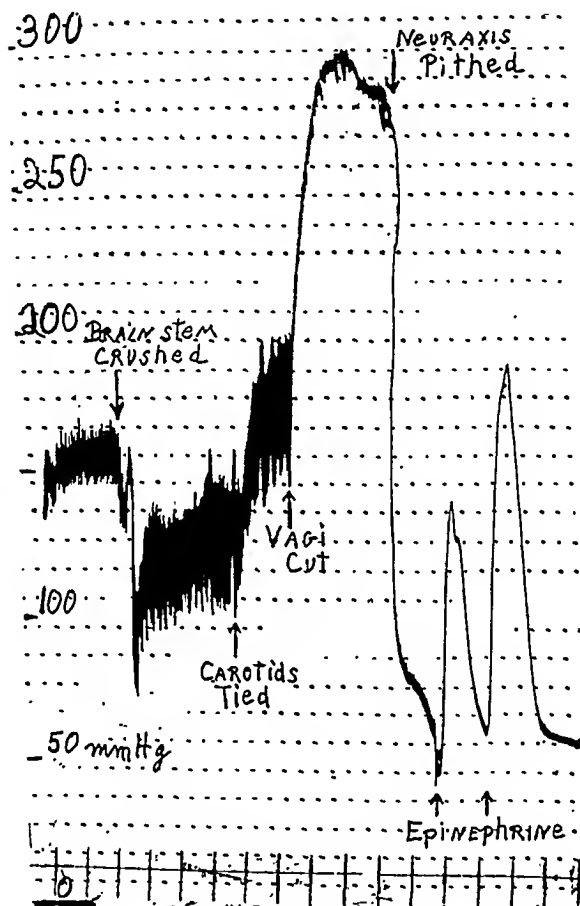


Fig. 4.—Arterial pressure curve, Dog H 2, Table II.

Peripherally acting vasoconstrictors, by raising arterial pressure, stimulate the nerve endings in the carotid sinus and great vessels, initiating reflexes which inhibit the outflow of vasoconstrictor stimuli from the vasomotor center. If one piths a rabbit or dog when it is hypertensive from the injection of such drugs as renin or epinephrine, no fall in pressure occurs because nervous vasoconstriction is already completely inhibited.<sup>2</sup> Under these circumstances, control over the circulation by the vasomotor center ceases once the pressure has been raised well above the normal level by a peripherally acting vasoconstrictor. In renal hypertension, both in man and animals, no loss or decrease in vasomotor control occurs; the pressure still rises in response to cold, pain, or loss of moderator nerve function; the flow in skin and muscles is still in-



creased in response to warmth or exercise. It therefore seems more reasonable to assume that the renal pressor hormone, in the concentrations reached in man and animals, in even the worst renal hypertension, does not act directly on the arterioles or usurp control from the vasomotor center, but acts to modify this control, i.e., to "set" the center for a high level. The effect of the kidney with an altered circulation upon the vasomotor center then can be likened to that of a myocardial infarct on the heat-regulating center. The latter causes fever, the former, hypertension, by changing the "set" of the control mechanism. However, this nervous mechanism in hypertension cannot be proved simply by lack of evidence of a peripheral vasoconstrictor; it must be ascertained whether the central nervous system, isolated from the general circulation and perfused by a renal hypertensive animal, will show such an altered vasomotor "set."

#### SUMMARY

Dogs with renal hypertension maintain arterial pressures above those of controls when, in both groups, the brain stem has been crushed rostral to the pons, or the spinal cord severed and destroyed below C<sub>4</sub>.

Removal of moderator nerve impulses by carotid ligation and vagal section causes as marked and striking a rise in pressure in dogs with renal hypertension as it does in normal dogs. Renal hypertension is not due simply to partial inhibition of moderator nerve influences, for, if it were, complete loss of inhibition would result in the same pressure in controls and hypertensives.

Complete destruction of the central nervous system lowers the arterial pressure of dogs with renal hypertension to the same level as that of controls similarly treated; there is no evidence of a circulating, peripherally acting vasoconstrictor substance.

It is concluded that, in animals and man, the renal pressor hormone acts through the vasomotor nervous control mechanism; that it "sets" the center for a high level and does not act directly on the arteries.

I wish to express my indebtedness to Professor Hanzlik for the use of the facilities of the Department of Pharmacology.

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## THE NORMAL DURATION OF THE Q-T INTERVAL

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A NUMBER of empirical formulas have been proposed to express the relation between the heart rate or cardiac cycle length and the Q-T interval of the electrocardiogram. The best known are those of Fridericia and Bazett. Fridericia<sup>1</sup> gave the duration of Q-T as  $K\sqrt[3]{C}$ , in which C is the R-R interval, or cycle length, and K is a constant, 8.22. This formula was found suitable by Schlomka and Raab,<sup>2</sup> who, however, state that K is 7.0 for infants, 7.95 for young people, and 8.25 in the aged. Bazett<sup>3</sup> proposed the formula  $Q-T = 0.37 \sqrt{C}$  for men, and  $Q-T = 0.4 \sqrt{C}$  for women. Fenn,<sup>4</sup> using the square root formula, employed a constant of 0.39 for both men and women. Several later authors<sup>5</sup> have agreed that these formulas are substantially accurate. A recent study indicates that Bazett's formula is more nearly in accordance with the facts when the heart rate is rapid and that Fridericia's applies when the rate is slow. Lipeschkin<sup>6</sup> says that the Q-T interval, as calculated, is too long by either formula when the heart rate is from 40 to 50 per minute. In rather sharp disagreement with others is Adams,<sup>7</sup> who, on the basis of the measurement of the Q-T intervals of fifty-one men and fifty-nine women, proposes the formulas,  $Q-T = 0.1536 R-R + 0.2462$  for men, and  $Q-T = 0.1259 R-R + 0.2789$  for women.

### METHOD

In view of the fact that logarithmic formulas fit closely the course of many biologic processes, it seems remarkable that, so far as we can learn, no such formula has been proposed, except by Ashman and Hull.<sup>8</sup> In order further to test the validity of the formulas given by them, over 1,000 electrocardiograms on 432 men, 425 women, and 226 children were measured. The ages of the children ranged up to 14 years, and very few infants were included. The electrocardiograms were taken by means of a Hindle-Williams electrocardiograph over a period of twelve years.

Many of the tracings were from normal subjects, i.e., medical students and interns. The rest were from hospital patients who showed no electrocardiographic or other evidence of heart disease, with two exceptions. Since our experience had demonstrated that thyrotoxicosis, in the absence of heart disease, does not affect the Q-T interval, over sixty patients with this disease, nearly all women, were included in order to augment the number with short cardiac cycles.

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In order to make certain that this procedure was valid, the average value of the constant,  $K$ , in these cases, and the value of  $K$  for an equal number of normal subjects whose heart rates were in the same range were calculated. There was no significant difference between the averages.

A similar, but less rigorous, selection of normal subjects appears at the other end of the scale. Again, in order to augment the number, a considerable proportion of these records were taken on elderly patients, mostly men, who were suspected of having arteriosclerotic heart disease, but had no history of heart failure or cardiac infarction and had normal electrocardiograms and normal blood pressure. Our experience has indicated that in these cases the Q-T is nearly always within the normal range. All patients with hypertension were excluded. When sinus arrhythmia was present, the average cycle length was taken. Except among children, only a few measurements were included when the arrhythmia was conspicuous. Most of the shortest cycles (below 0.38 sec.) are from patients with supraventricular paroxysmal tachycardia.

The Q-T intervals of the adults were measured to the nearest 0.005 sec. by use of a hand lens. The average value of the measurements of several cycles was recorded. Care was taken to include the duration of the Q wave in the interval, no matter how inconspicuous that wave was. In nearly all cases, Q-T was measured in the lead with the highest T wave. Cycle lengths were measured to the nearest 0.01 sec. Among the adults, about a dozen wholly inadvertent duplicate readings were made on the same patient at different times. The children's Q-T intervals included forty to fifty duplicates. Fifty per cent of the data on children were taken from the measurements of Hafkesbring, Drawe, and Ashman,<sup>9</sup> and to the nearest 0.01 sec. Many of the same group, and a large additional number, were measured by the author, and all of the measurements were used.

## RESULTS

Since it was found that, on the average, Q-T is slightly longer in the older subjects, we first present the data on all males between the ages of 15 and 32, inclusive. In Fig. 1 the data are averaged, and each point represents the cases included within a cycle length of 0.05 sec. The figures indicate the number of individual measurements which were averaged for each point. In deriving the average, points which fell, for example, on both cycle 0.725 sec. and cycle 0.775 sec., were included in the average for cycle 0.75 sec. Therefore, the sum of the numbers slightly exceeds the total number of cases. The curve is calculated from the formula,  $Q-T = 0.375 \log [10(C + 0.07)]$ . This is the formula of Ashman and Hull<sup>8</sup> for men and children. It gives a very satisfactory, although not perfect, approximation of the data. If  $K$  is taken as 0.373, the agreement is slightly better. The very similar formula,  $Q-T = 0.370 \log [10(C + 0.09)]$  fits the data a little more closely.

Fig. 2 gives the data for all the females in the same age range. The formula of the curve is that given by Ashman and Hull for women, i.e.,  $Q-T = 0.385 \log [10(C + 0.07)]$ . Here the agreement is almost perfect.

Fig. 3 combines the data for males and females between the ages of 15 and 32 years. In the construction of this curve, the individual female Q-T measurements were reduced, at each cycle length, by the vertical distance between the curves for men and for women, as given by Ashman and Hull. Fig. 3 is drawn from the formula,  $Q-T = 0.375 \log [10(C + 0.07)]$ ; this is the same as the formula previously given for men. For comparison, curve *B* is Bazett's formula, using the constant 0.39. Curve *C* is Fridericia's, with a constant of 8.0.

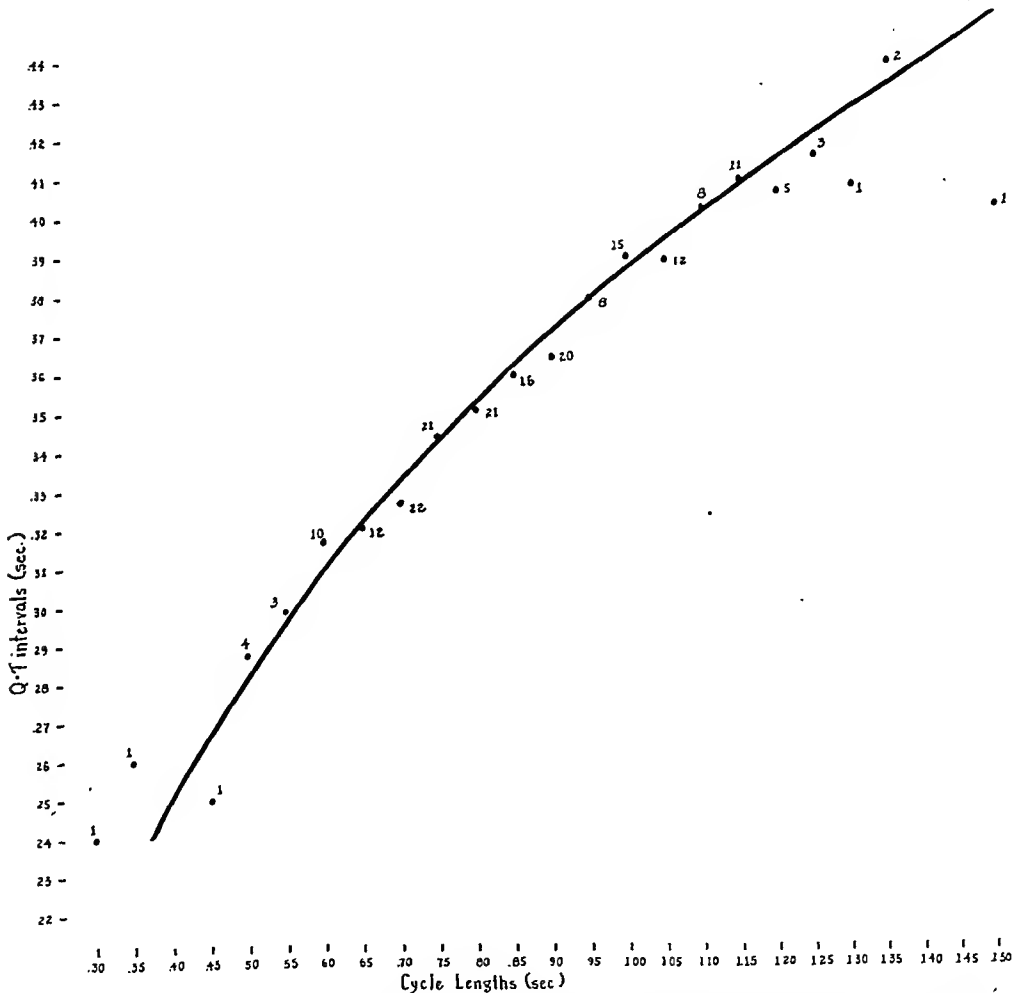


Fig. 1.—Young adult males. Each point is the average duration of Q-T in an interval of cycle length of 0.05 sec. The numbers indicate the number of cases included in each average. The curve is drawn to the formula,  $Q-T = 0.375 \log [10(C + 0.07)]$ .

When the measurements on all subjects 45 years of age, and older, are similarly treated, the curve, using a constant of 0.380, fits the average data closely.

Fig. 4 shows the scatter diagram for all the adult subjects. The curve which is drawn in uses a constant of 0.375. The agreement is excellent from cycle 0.40 sec. to cycle 1.00 or 1.10 sec. Beyond, the points range somewhat above the curve. A logarithmic curve will apparently not fit these data accurately and should not be expected to do so, for the averages at the longer cycle lengths include very

much higher percentages of middle-aged and elderly persons than those at shorter cycle lengths. Because of the influence of the disproportionate number of these older persons, the averages do not follow the curve but drift above it at slow heart rates.

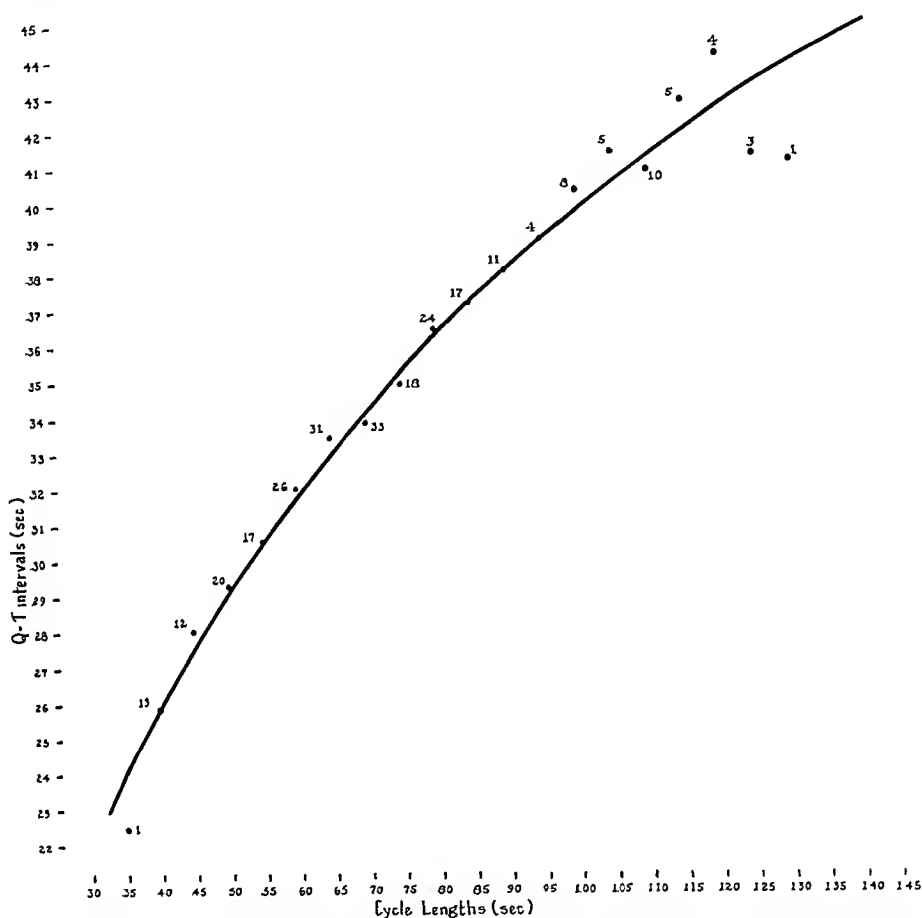


Fig. 2.—Young adult females. The formula for the curve is  $Q-T = 0.385 \log [10(C + 0.07)]$ . Otherwise as Fig. 1.

A curve drawn according to Ashman and Hull's formula for women, i.e.,  $Q-T = 0.385 \log [10(C + 0.07)]$ , agrees very well with the data for all women, except at long cycles, where the influence of a disproportionate percentage of older persons again affects the average.

The data for children are less complete than for adults, but the curve fits the data fairly accurately. There are at least three factors which render the children's data less reliable than the adults'. One is the lack of a sufficient number of measurements at the extremes of heart rate. The second is that the frequency of sinus arrhythmia leads to error when the average cycle length is calculated, for the average on a short record may not be the true rate over a longer period of time. More important is the fact that the child is often more nervous than the adult, so that the heart may accelerate just before the record is obtained. With such

an acceleration, Q-T does not adjust itself immediately to the new rate; this fact has been recently re-emphasized by Blair, Wedd, and Young.<sup>10</sup> For boys of all ages, and for girls to the age of 12 or 13, the average value of K is 0.375. If the disturbing influences which have been noted were eliminated, the value would probably be the same as that for young adults. Mannheimer,<sup>11</sup> using Ashman and Hull's formula, has found that it fits his children's data very closely.

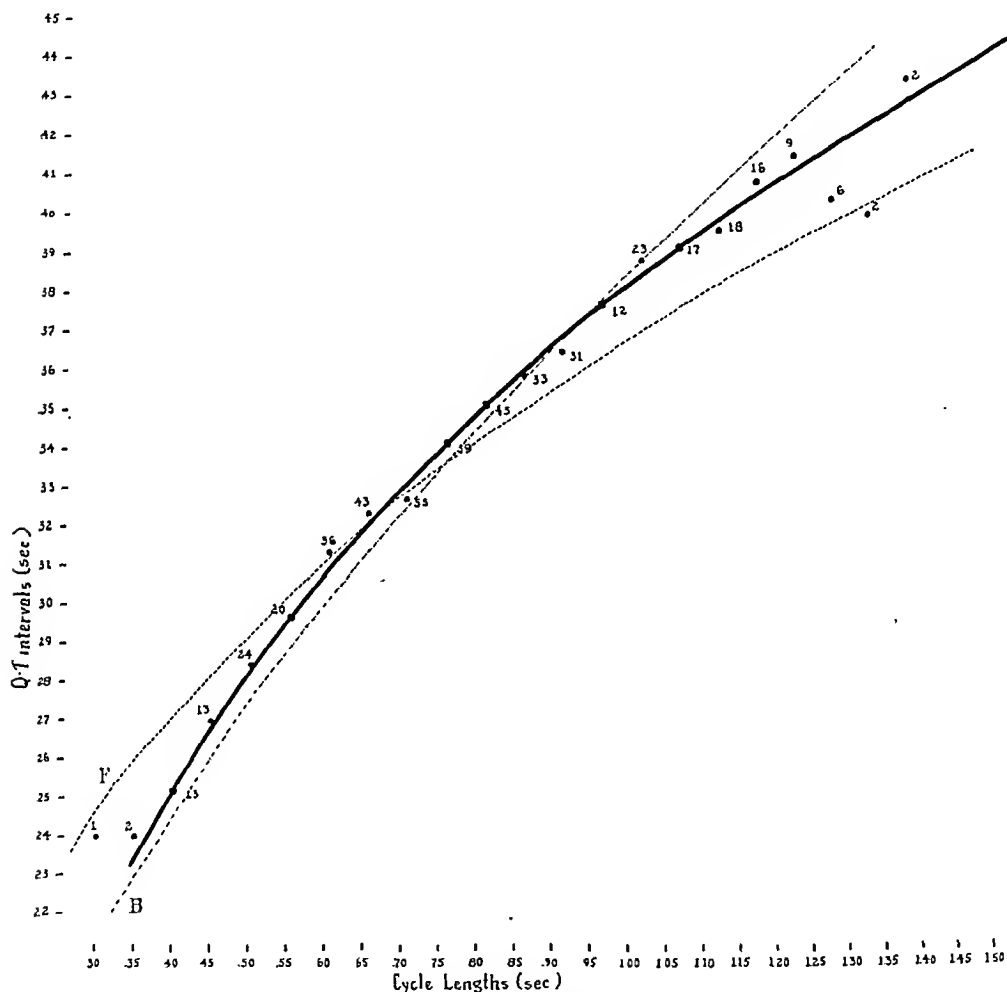


Fig. 3.—All normal subjects, aged 15 to 32 years; the points for women were lowered by the vertical distance between the curve for men, using  $K = 0.375$ , and, for women, using  $K = 0.385$ . *F* is Fridericia's curve, using a constant of 8, and *B* is Bazett's curve, using a constant of 0.29.

Fig. 5 represents the results of measurements of nearly 700 intervals from patients with heart disease. The arteriosclerotic-hypertensive etiology was predominant. The formula for the curve is  $Q-T = 0.405 \log [10(C + 0.07)]$ . The Q-T intervals of the women were reduced by the distance between the curve for women with heart disease ( $K = 0.410$ ) and that of men with heart disease ( $K = 0.405$ ). This curve is included merely to demonstrate that here, also, a logarithmic curve fits the data closely. It may be noted that, when prolongation occurs, it is nearly, and perhaps precisely, in proportion to the Q-T

length characteristic of each cycle length. In other words, the lengthening is not by an absolute amount, such as, for example, 0.04 sec., at all heart rates.

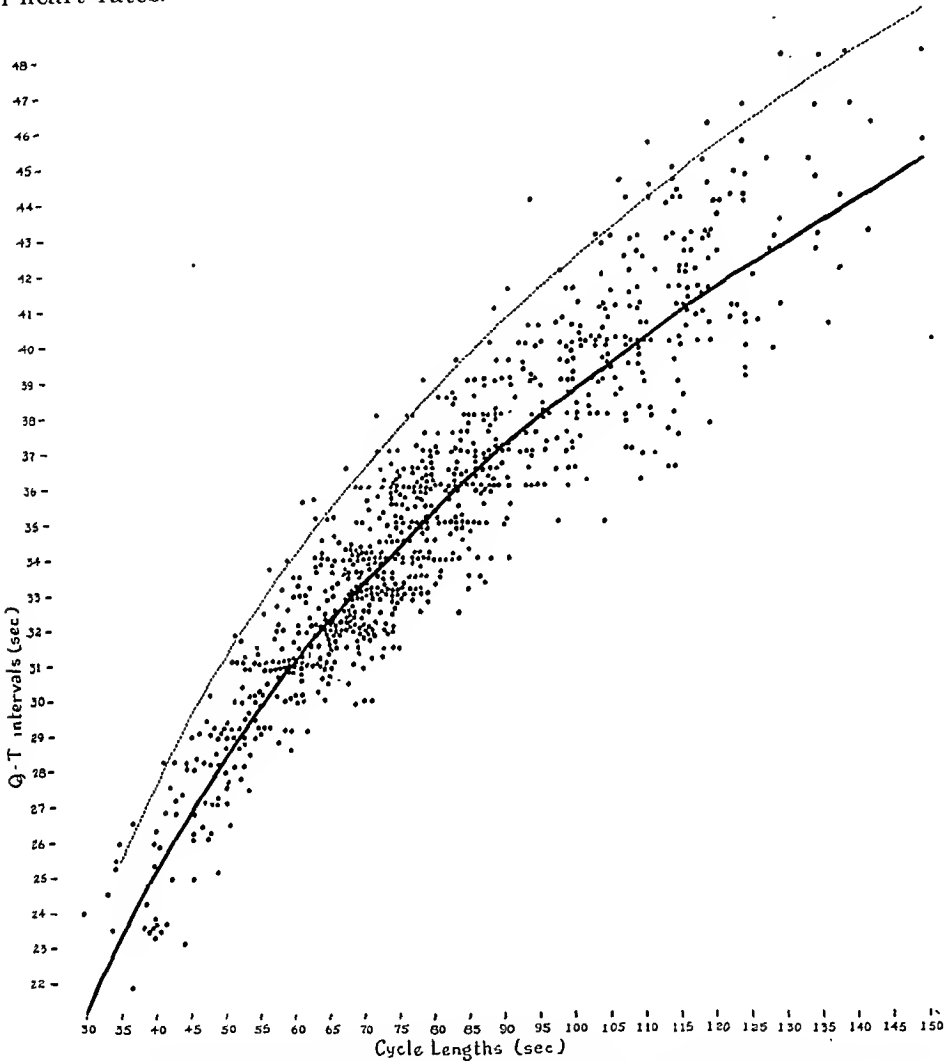


Fig. 4.—Scatter diagram of all adult subjects. Solid curve as in Figs. 1 and 3. Dotted curve is drawn from the same formula, using  $K = 0.41$ .

The upper limit of the normal Q-T interval was given by Ashman and Hull as a curve defined by a constant of 0.41 for men and 0.42 for women. In Fig. 4, the light, dotted line corresponds to the formula  $Q-T = 0.41 \log [10(C + 0.07)]$ , i.e., the upper limit for men. Since the points for women have been corrected to the male level, this formula will also apply to the women in this figure. It will be noted that only thirteen, or 1.5 per cent, of the points lie above this line by more than 0.005 sec.; this figure is within the error of measurement. Most of these longer intervals were from subjects over 33 years of age. This observation confirms the validity of the curve for the upper limits of the normal



as they were given. In this connection, it should be noted that this curve applies only to records in which the duration of the QRS complex is within normal limits.

The constant,  $K$ , can readily be ascertained for each individual interval by dividing the Q-T interval by  $\log [10(C + 0.07)]$ . This has been done for all of the subjects. The frequency distribution of  $K$  for men and for women is shown in Fig. 6.

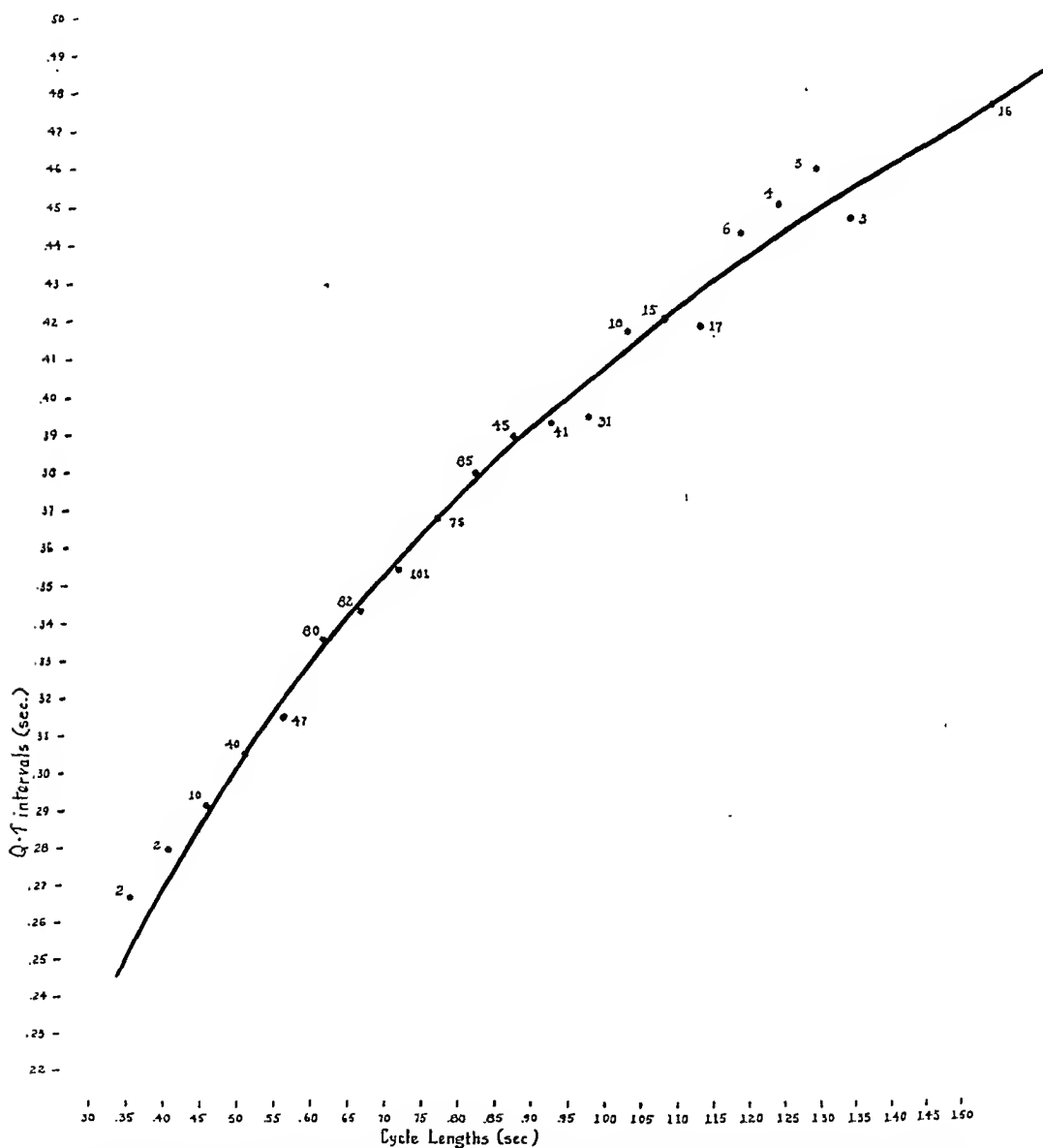


Fig. 5.—Averages of subjects with heart disease, predominantly of arteriosclerotic-hypertensive etiology (excluding thyrotoxicosis). Women's Q-T intervals adjusted. The formula for the curve is  $Q-T = 0.405 \log [10(C + 0.07)]$ .

In Table I the average values of  $K$  for 428 men and 412 women whose ages were known are given. Four cases of paroxysmal tachycardia among the men, with constants of 0.423, 0.418, 0.414, and 0.404, respectively, and four among the women, with constants of 0.425, 0.423,

0.393, and 0.391, respectively, are omitted from the averages for reasons given below. The average value of K for all the men was 0.377, and, for the women, 0.387. When these groups were subdivided according to age, the shortest average constants were found in the youngest groups. The difference between men and women is obviously statistically

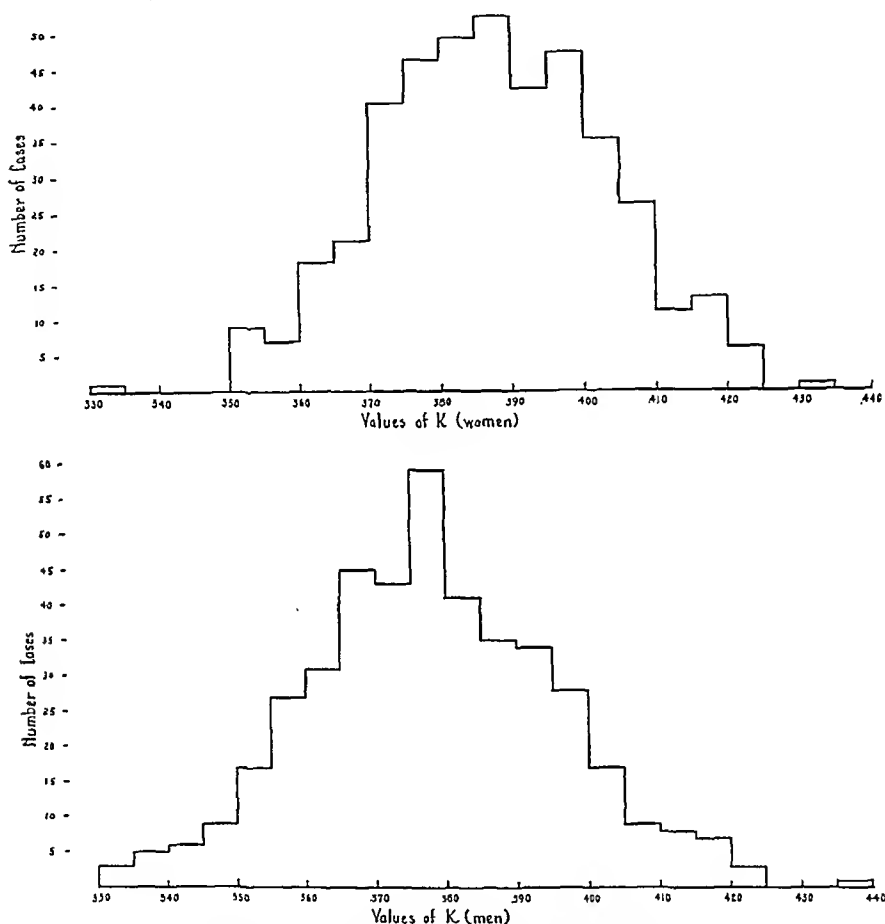


Fig. 6.—Frequency distribution polygons of the values of K for all the men (below) and all the women (above).

TABLE I

| AGE<br>(YEARS) | MEN |       | WOMEN |       |
|----------------|-----|-------|-------|-------|
|                | NO. | AV. K | NO.   | AV. K |
| All            | 428 | 0.377 | 412   | 0.387 |
| 15-32          | 193 | 0.373 | 244   | 0.385 |
| 33-44          | 112 | 0.380 | 117   | 0.388 |
| 45 and over    | 123 | 0.380 | 51    | 0.390 |

significant and is reported by most of the students of this subject. The significance of the difference between the younger and the two older male groups has also been calculated. The probable error of the latter difference is  $\pm 0.0011$ , or less than one-sixth of the difference between the means.

The average value of  $K$  for 116 boys was 0.375, and, for 110 girls, 0.377. The age ranges for boys and for girls were from a few days to 15 years, and from a few days to 14 years, respectively. The difference between the average constants of boys and girls is too slight to be significant, but it is interesting to note that the average constant for the thirty-two girls between the ages of 12 and 14 years, inclusive, was 0.380. Their exclusion would reduce the average for girls practically to the average for boys. The prolongation of the Q-T interval from that of the child to that of the woman seemingly begins not later than at the age of 12 or 13. Although the mean value of  $K$  of the younger children tended to be shorter than that of older ones, no significant difference was found. Our figures suggest that, in early infancy, the Q-T may be slightly shorter, but a significant difference could not be established without a much larger number of measurements of normal infants. This is also suggested by Mannheimer's figures for children, mainly infants, with congenital heart disease.<sup>11</sup>

On the other hand, some of our intervals at higher heart rates may have been measured during a period of transitory acceleration caused by nervousness of the subject. This factor would tend to render these intervals slightly too long. The true curve, as ultimately constructed, may, therefore, be slightly, but perceptibly, steeper than the present one, and a slight adjustment of the constants may be required.

The difference according to age is much less than that reported by Sehlomka and Raab,<sup>2</sup> who used Fridericia's formula. The large difference they observed between young children and adolescents, corresponding to constants of 7.0 and 7.95, respectively, almost certainly was due to their use of the cube root formula. This formula makes the calculated values for the more rapid hearts much too high. Consequently, in young children, whose average heart rates are high, a low constant must be used to force the curve to fit the average of the data.

Shipley and Hallaran<sup>5</sup> published scatter diagrams of 100 normal men and 100 normal women. The average  $K$  for both groups was calculated by us. That for the men was found to be 0.380, and, for the women, 0.393. The logarithmic curve given herein, using these constants, will be found to conform closely to their data. It is worth noting that the difference in  $K$  between men and women in Shipley and Hallaran's cases was 0.013; the difference between the constants for our younger subjects was 0.012. If the upper limit of the normal Q-T be placed at  $K = 0.410$  for men, and 0.420 for women, one of Shipley and Hallaran's men reaches this limit and none exceeds it. On the other hand, four of their women exceed the upper limit, with constants of 0.443, 0.428, 0.424, and 0.421, respectively. Since, however, Shipley and Hallaran's measurements of Q-T were consistently slightly longer than those herein reported by about 0.01 sec., the upper limit for women should be raised,

to accord with their technique of measurement, to about 0.430. This would leave only one abnormally long Q-T interval in their group of 200 subjects.

White and Mudd<sup>17</sup> published a scatter diagram relating the Q-T interval of forty men, women, and children to the heart rate. If the rates are expressed in terms of cycle lengths, it will be found that their data also conform closely, except at the extremes of heart rate, to the logarithmic formula proposed herein if one uses a constant,  $K$ , of about 0.363 instead of 0.375. It will be observed that, although Shipley and Hallaran's Q-T measurements slightly exceed those herein reported, those of White and Mudd are considerably shorter.

#### DISCUSSION

The use of one formula for all human hearts may be criticized because the human curve is composite, representing many different persons, and may therefore not at all represent the curve as it might be derived from one heart. In fact, there is evidence<sup>13, 17</sup> that, if such a curve is constructed from one person's heart and the rate is varied by exercise or other procedures, the same slope is not always followed. But this work is open to the interpretation that, after a new rate has been attained, the rate must be kept at the new level for some time before equilibrium is established. Thus, the Q-T intervals during paroxysmal tachycardia were distinctly longer, on the average, than the calculated values, whereas, in thyrotoxicosis, even with almost equally rapid rates, the Q-T average was very close to that calculated. In the case of one male, a young physician with no evidence of heart disease, the Q-T interval during the paroxysm was nearly 0.03 sec. above the calculated value. After the paroxysm, at a cycle length of 0.65 sec., the Q-T was 0.28 sec., or 0.04 sec. shorter than the calculated value. In fact, it was shorter by 0.02 sec. than the Q-T of any other subject at this cycle length. On another occasion, the same subject had an electrocardiogram taken long after his last paroxysmal attack. The cycle was 0.655, and the Q-T, 0.32 sec., or just at the average length for men. We interpret this to mean that, after the paroxysm, a considerable period of time (more than enough to record all three leads) was required for the Q-T to lengthen to normal; whereas, during the paroxysm, insufficient time may have elapsed when the record was taken for the Q-T to have shortened to the characteristic length. On the other hand, it is possible to find electrocardiograms which show a rather prompt adjustment.

In any event, when electrocardiograms are taken under different conditions, as before and after meals, just after ordinary activity, while reclining, etc., the Q-T interval will vary with the heart rate at least approximately as the formula shows.<sup>17</sup> Since the phenomenon with which we are dealing is a fundamental one and since all human hearts are composed of practically the same protoplasm, we may anticipate

that a curve of Q-T intervals derived from a large number of persons with different heart rates will be of the same type (logarithmic) as a curve derived from a single subject, providing, of course, that, at each heart rate, equilibrium has been established.

It has been demonstrated that one of the factors which determine the duration of the Q-T interval is the blood calcium level.<sup>14, 15, 17</sup> As the ionized calcium level rises, the Q-T interval shortens, and vice versa. Intravenous injection of metaphosphate, which prevents the ionization of calcium salts, will markedly lengthen the Q-T interval in the dog. In the *Nitella* cell, according to the theory proposed by Osterhout and Hill,<sup>12, 16</sup> the action current is related to the movement of potassium ions. Perhaps the ionized blood calcium modified the Q-T interval by virtue of its well-known "antagonism" to potassium.

It is by no means established that the only factor responsible for prolongation of the Q-T interval in man is a decrease in calcium ions, even though it is probably true that the more conspicuous prolongations are associated with a low blood calcium. Heart disease, by disturbing the ionic balance in the cell, may possibly also prolong the Q-T interval. The Q-T interval is moderately prolonged in many cases of hypertension and aortic insufficiency, and is often more definitely increased in myocardial infarction after the acute stage. This is not due to widening of the QRS interval. Is the blood calcium reduced in these cases? In acute rheumatic carditis and among children who are convalescent from diphtheria, moderate prolongation of the interval is very common. It remains to be seen how important this is clinically, but it is my belief that this sign is very helpful in cases of suspected rheumatic carditis or myocardial ischemia. It has been pointed out that the sign may be useful in the diagnosis of uremia. If the interval proves to be of clinical value, it certainly becomes important to know accurately the normal relation between it and the cycle length and to know the normal range of variation.

Statistical methods have been applied in the study of our data only as indicated above. They are not needed when the quantity of data is adequate. The paper on this subject which makes most use of the statistical method<sup>7</sup> is easily in the poorest agreement with the observations of all other authors. Without at all decrying the application of statistical methods, which have great usefulness, the paper mentioned provides an example of the misleading sense of security which may be engendered by the use of the method with data which are insufficient. If the number of careful measurements were to be increased to, say, 10,000 and were evenly distributed throughout the range from cycle 0.30 to cycle 1.50, the curve would outline itself in the more densely packed areas at the median Q-T for each cycle length, and its definition, logarithmic or otherwise, would be a mere formality.

## SUMMARY

The curve which expresses the relation between heart cycle length and the duration of the Q-T interval is logarithmic.

It may be represented by the general formula  $Q-T = K \log [10(C + k)]$ , in which  $C$  is the cycle length (R-R) in seconds.  $K$  and  $k$  are constants. The formula for women between the ages of 15 and 32 years, inclusive, is obtained by using  $K = 0.385$  and  $k = 0.07$ .

The formula for younger men, and for children after early infancy, is derived by using  $K = 0.375$  and  $k = 0.07$ . In these cases a slight change in both constants may possibly yield somewhat better agreement, but it is convenient and introduces a hardly appreciable error to use  $k$  as for women.

To patients 45 years of age, or older, the same formula applies, but with a  $K$  of 0.380 for men and 0.390 for women.

The upper limits of the normal Q-T interval may be expressed by the formulas previously published,<sup>8</sup> with allowance for personal variations in the technique of making the Q-T measurements.

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## RAYNAUD'S DISEASE

### A REVIEW OF ITS MECHANISM, WITH EVIDENCE THAT IT IS PRIMARILY A VASCULAR DISEASE

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SINCE Raynaud described the disease which bears his name there has been a difference of opinion concerning whether the disease is primarily one of the sympathetic nervous system or of the vascular system. With the help of information which we have obtained from studies on nonvasospastic patients after sympathectomy, we have attempted to elucidate some of the problems concerning the relationship of the sympathetic system to the cutaneous vessels. We are reporting three cases of Raynaud's disease, with special studies.

#### CASE REPORTS

CASE 1.—F. C., a white man, 55 years old, entered the hospital Aug. 4, 1938, with the complaint of cold, painful hands and feet. He stated that for the preceding four or five years his hands and feet would become numb and white and would ache and sting when exposed to cold. He had found it necessary to take the special precaution of wearing several pairs of woolen garments.

*Examination.*—The patient was of average weight and height, and appeared normal. He did not seem nervous or emotionally unstable. The general physical examination was essentially negative except for the fact that he was edentulous and had been operated on for relief of a hydrocele on the right side. Temperature was 98.6° F.; pulse rate, 72; respiration, 18. The blood pressure was 125/80 in both arms.

His fingers and toes felt cool, but did not appear particularly abnormal at room temperature. After immersing his hands in ice water for thirty seconds, there were scattered areas of blanching on the palms, and the skin over the distal two phalanges of the fingers became pallid. This color change was accompanied by aching and stinging pain. Two to three minutes after the hands were removed from the water the blanching disappeared.

On a previous admission to the hospital, April 2, 1938, an ice water test was done. Blanching of the fingers occurred when they were in the ice water, but the color returned to normal at room temperature. He was taken outdoors, where the atmospheric temperature was 20° F. His fingers became extremely pale; there was the usual aching pain; and, in fifteen minutes, the color changed through a red to a cyanotic hue.

The radial, popliteal, posterior tibial, and dorsalis pedis pulses were present, equal, and of good quality on the two sides. There was no evidence of trophic change on the fingers and toes.

*Laboratory Study.*—The urine and blood were normal. The blood Wassermann reaction was negative.

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*Diagnosis.*—Raynaud's disease (confirmed by Dr. Edgar V. Allen).

*Treatment.*—X-ray irradiation of the sympathetic chains was advised, but, since there was some question concerning the efficacy of irradiation, it was finally decided to do a cervicodorsal ganglionectomy on one side, and irradiate the other side.

On Aug. 6, 1938, the left inferior cervical and first and second dorsal ganglia were removed. This was followed by a Horner's syndrome on the left, and the left hand became obviously warmer than the right. The aching, stinging pain incident to exposure to cold was abolished on the left.

Recovery was uneventful, and he subsequently received 1,200 roentgen units over the corresponding ganglia on the right side. No evidence of subjective or objective improvement was observed as a result of the irradiation. He was discharged Aug. 22, 1938.

#### FOLLOW-UP EXAMINATION AND SPECIAL STUDIES

The patient returned to the hospital March 25, 1940, approximately twenty months after his operation. His general condition was essentially the same as on the previous admission, except that he felt that his feet and right hand were growing worse, i.e., he had more pain on exposure to cold. His left hand had been entirely devoid of pain since the operation.

The difference in the temperature of the fingers on the two sides varied from time to time at room temperature. At times there was no difference, and at others, the fingers of the left hand were 4.5° C. warmer than those on the right. Only on one occasion (before the adrenaline test) were the third, fourth, and fifth fingers slightly colder on the left side.

A thermoregulatory sweating test revealed absence of sweating in the usual distribution after removal of the inferior cervical and first and second dorsal ganglia. This included the left side of the face, neck, upper extremity, and chest down to the level of D 3. There was no evidence that regeneration had occurred.

We studied the skin temperature in the heating cabinet, refrigerator, after intravenous injection of adrenaline, and after administration of pilocarpine. The results are incorporated in Tables I, II, and III.

TABLE I

THE EFFECT OF HEAT (INDUCTOTHERM PLUS ATROPINE) ON THE SKIN TEMPERATURE

| TIME (P.M.)                                       | 3:10                 |      | 3:12                                   | 3:16       | 4:20                  |      | DIFFERENCE<br>IN FIRST<br>AND LAST<br>READINGS |     |
|---|----------------------|------|--|------------|-----------------------|------|--|-----|
|   | RIGHT                | LEFT |  |            | RIGHT                 | LEFT |  |     |
| Skin temperature<br>average for<br>fingers (° C.) | 4.3                  | 7.2  |  |            | 9.0                   | 9.0  | 4.7  | 1.8 |
| Mouth temperature                                 | 37.0° C.<br>98.6° F. |      |  |            | 38.0° C.<br>100.4° F. |      |  |     |
| Pulse rate  | 88                   |      |  |            | 144                   |      |  |     |
| B.P.  | 140/80               |      |  |            | 120/70                |      |  |     |
| Remarks   | Basal                |      | Atropine,<br>gr. $\frac{1}{75}$<br>(H) | In cabinet |                       |      |  |     |

Room temperature, 26.0° C.; cabinet temperature, 45.5° C.

#### METHOD

Skin temperatures were taken with the Tycos dermaterm.\* Before beginning an experiment, the patient was exposed from twenty to thirty minutes at a constant

\*Taylor Instrument Co., Rochester, N. Y.



room temperature, after which basal readings on various skin zones were taken. The mouth temperature, pulse rate, and blood pressure were followed throughout each experiment, and all observations recorded. The junction thermocouple was checked for each set of readings, and appropriate corrections were made, although this was rarely necessary. The figures recorded in the tables are the dermatherm readings, and hence indicate only the relative changes in temperature.

TABLE III

EFFECT OF PILOCARPINE ON SWEATING AND SKIN TEMPERATURE, MARCH 28, 1940

| TIME (A.M.)                                       | 11:45                |      | 11:50   | 12:32                |      | DIFFERENCE<br>IN FIRST<br>AND LAST<br>READINGS |      |
|---|----------------------|------|---|----------------------|------|--|------|
|   | RIGHT                | LEFT |   | RIGHT                | LEFT | RIGHT  | LEFT |
| Skin temperature<br>average for fingers<br>(° C.) | 2.5                  | 6.5  | Pilocarpine, gr. $\frac{1}{32}$ ,<br>hypodermically | 0.5                  | 6.6  | -2.0   | 0.1  |
| Mouth temperature                                 | 37.0° C.<br>98.6° F. |      |   | 36.4° C.<br>97.5° F. |      |  |      |
| Pulse rate  | 72                   |      |   | 76                   |      |  |      |
| B.P.  | 128/90               |      |   | 130/90               |      |  |      |
| Remarks   | Basal                |      |   |                      |      |  |      |

Room temperature, 25.5° C.

*Comment on Heating Experiment.*—We used the Burdick heating cabinet, i.e., dry heat and inductotherm. We have found that the administration of atropine in conjunction with the inductotherm results in the most marked dilator response of cutaneous vessels.<sup>1</sup> The inductotherm is so arranged that it affects the entire body.

At the beginning of the experiment the only significant difference in the temperature on the two sides of the body was of the finger tips, which were 2.9° warmer on the left. At the end of the heating experiment the temperature of the fingers was the same on the two sides. The mouth temperature rose 1.8° F. There was a fair amount of sweating toward the end of the experiment, except in the sympathectomized zone. There was marked capillary flushing which was limited to the right side of the face, right ear, and right hand. The line of demarcation between the flushed and unflushed zones on the face was definite. The significance of this phenomenon has been discussed.<sup>1</sup>

In this, as well as in the succeeding three experiments, the temperature changes of the forehead, ears, nose, cheeks, neck, chest, arms, forearms, palms, abdomen, thighs, calves, ankles and toes were also recorded. Since they revealed nothing particularly significant they were not included in the tables.

*Refrigerator Experiment.*—The method of carrying out this test has been given.<sup>2</sup> The patient is taken into the refrigerator nude, except for a loin cloth. At the beginning of the experiment the temperature of the fingers on the left side was 2.9° higher than on the right. At the end of the experiment the fingers on the left were still 1° warmer than those on the right, but actually the temperature of those on the left decreased over a greater range than on the right. Fig. 1 shows the fall in temperature of the fingers on the two sides (the readings are the average for five fingers). It can be seen that, after fifty minutes in the refrigerator, the temperature of the sympathectomized fingers dropped almost as low as did that of the unsympathectomized fingers. Indeed, at the end of the experiment the temperature on the two sides was more nearly equal than had been the case when the same experiment was done on nonvasospastic patients.<sup>2</sup> At any rate, we feel the important fact under the circumstances of this experiment, in which the whole body is exposed to cold, is that the sympathectomized fingers become almost as cold

objectively as the normally innervated ones. If the sympathetics had been playing a greater than normal role in this case, one would expect the intact side to show more vasoconstriction than that which had been operated on.

The subject began to shiver on entering the refrigerator, and continued to shiver until the end of the experiment. After fifteen minutes in the refrigerator both hands became blanched, the right slightly more so. After another five minutes the palms of both hands developed islands of mild flushing, with areas of pallid skin between. At the end of the experiment there was a mild, pink flushing of the hands, except for the distal two phalanges of all fingers. The latter were quite pallid, and remained so for one-half hour after being exposed to room temperature. The difference in the appearance of the two hands was one only of degree. The sympathectomized hand appeared only slightly less cyanotic in the nonblanched zones.

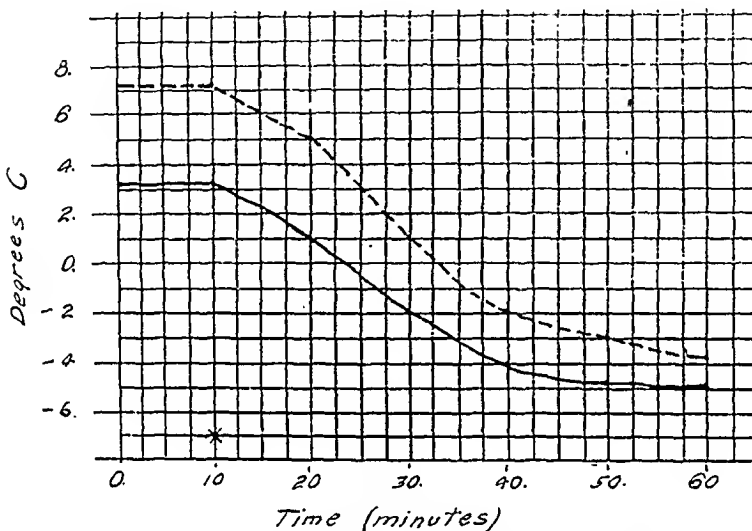


Fig. 1.—Graph illustrating the fall in the temperature of the fingers of F. C. in a refrigerator at 6° C. The temperature readings are those of the thermocouple, and are only relative. The basal readings were taken at room temperature (78° F.). Each curve represents the average for five fingers. The broken line represents the left (sympathectomized) hand. The unbroken line represents the right (intact) hand. \*, Time at which refrigerator was entered.

The left (sympathectomized) hand subjectively felt warm, comfortable, and devoid of pain throughout the experiment, whereas the right hand felt cold and ached and stung as if it were penetrated by "a thousand needles." The feet felt like the right hand. The painful sensation in the right hand was marked after ten minutes in the refrigerator, at which time the relative temperature of the thumb was 2.0°. Ten minutes later the relative temperature of the left thumb also measured 2.0°, but no pain was felt on the left then or at any other time.

*Comment on Adrenaline Experiment.*—At the beginning of the experiment the temperature of the fingers on the two sides did not differ greatly. It is interesting that ten minutes after the adrenaline was injected (right median basilic vein), the temperature of the fingers on the right side fell 4.7°, which was greater than the fall on the left. This may have been an emotional response. At the end of one hour and ten minutes the temperature of the fingers was very little different on the two sides.

*Comment on Pilocarpine Experiment.*—At the beginning of the experiment the temperature of the fingers on the left was 4.0° warmer than that on the right. At the end of the experiment the temperature of the fingers on the right showed a fall of 2.0°, whereas that of the fingers on the left showed very little change. This is in keeping with our observations on nonvasospastic subjects. Our impression is that pilocarpine causes forced heat dissipation by its peripheral action (sweating and

vasodilatation). This is usually accompanied, as demonstrated in this case, by a fall in central temperature. The heat conserving mechanism then reacts, with a resulting vasoconstriction and usually shivering. Hence the normally innervated side becomes colder, whereas the sympathectomized side, which is disconnected from the central mechanism, fails to respond.

The patient experienced a desire to defecate and urinate, and began to sweat on the right side of the face, chest, and arm at 12:06. There was no evidence whatever of sweating in the sympathectomized zone. At 12:02 he began to feel cold except in the sympathectomized zone. The latter felt warm subjectively. This patient did not shiver. Patients usually shiver during this test, and state that they feel colder and more uncomfortable than when in the refrigerator.

#### SUMMARY OF CASE 1 (F. C.)

A 55-year-old white man with Raynaud's disease was studied twenty months after removal of the inferior cervical and first two dorsal ganglia on the left. Skin temperature was studied with the patient in a heat cabinet, in a refrigerator, and after the administration of adrenaline and pilocarpine. The observations indicated that the sympathectomy was complete for the left side of the face and upper extremity. This was true as regards sweat glands and cutaneous vessels; there was no evidence of sympathetic nerve regeneration. Pilocarpine anhidrosis was equivalent to thermoregulatory anhidrosis, indicating that the sympathectomy was post-ganglionic.<sup>3</sup> During the administration of adrenaline intravenously the temperature of the sympathectomized fingers did not fall materially. In a refrigerator the patient's hands developed the characteristic color changes of Raynaud's disease, and there was practically no difference in the appearance of the two hands. The left hand, however, was devoid of pain and felt warm subjectively, as has been the case ever since operation. The right hand ached and stung and felt quite cold.

CASE 2.—E. V., a white woman, 43 years old, entered the hospital May 22, 1940, complaining of limitation of motion in the joints and painful, cold, and white fingers and toes. About three years earlier she began to notice that at times the skin over the first phalanges of the fingers would grow pale and feel numb, and this would be followed by aching and stinging. This would persist for several minutes, after which the color would change to blue and then to red. The fingers would become normal again in about fifteen minutes. The attacks at first occurred only in winter, but later came on in the summer months, as well. For three years the left knee, right elbow, shoulder, wrists, and phalangeal joints had been growing somewhat stiff and painful.

*Examination.*—Physical and routine laboratory examination revealed nothing abnormal except the appearance of the hands and feet and early atrophic arthritic changes in the elbows, wrists, and phalangeal joints. The patient was not "high strung," nervous, or emotional.

The hands and feet were cold to the touch, and presented a thin, shiny, smooth skin which was devoid of hair. There were no ulcerative changes; roentgenologic examination revealed generalized atrophy of the wrists, elbows, and knees, without evidence of narrowing of the joint spaces.

When the patient's hands were placed in cold water for fifteen to thirty seconds, or when she was taken into a refrigerator, the terminal two phalanges of the fingers, particularly the index, middle, and little fingers, became dead white. The color change was accompanied by aching and stinging pain. After two to five minutes at room temperature the appearance of the fingers became normal again. In the hospital the blue phase of the color change was absent, although the patient stated

that it had been present at other times. Nevertheless, we felt the syndrome was sufficiently characteristic of Raynaud's disease to warrant the diagnosis, and the following experiments were carried out with the idea of ascertaining what influence the sympathetics have on the skin vessels, and whether this influence could be overcome by exposing the hand alone to a warm temperature.

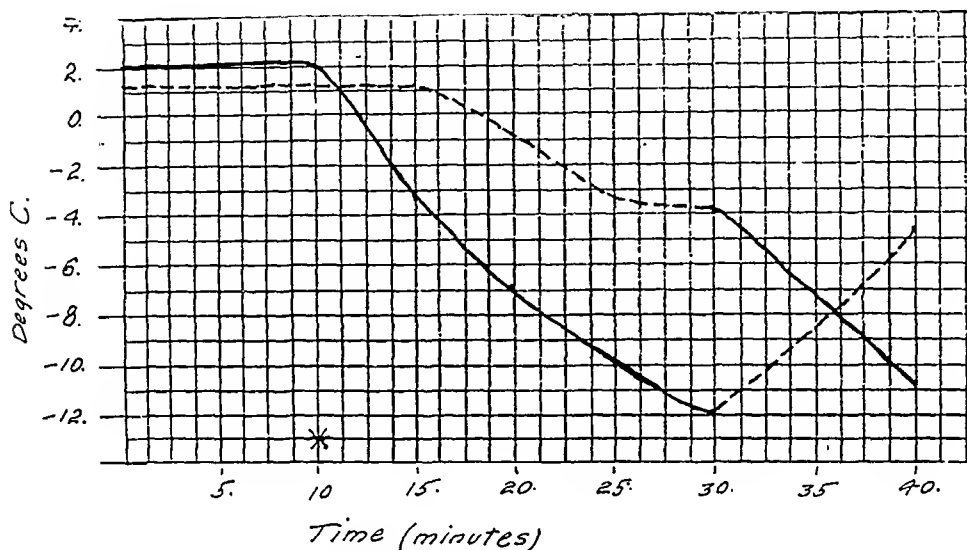


Fig. 2.—Patient E. V. was taken into a refrigerator, but her left hand was kept in a heated box. Curves represent the average skin temperature change of all fingers of each hand. Room temperature at which basal readings were taken, 25.0° C.; refrigerator temperature, 4.0° C.; temperature of heated box, 25.0° C.; solid line = right (exposed) hand; broken line = left (warmed) hand. \* Time at which refrigerator was entered. At the end of thirty minutes the right hand was placed in the warm box and the left was exposed.

*Experiment 1.*—We wished to expose the patient's body to severe cold, and, at the same time, keep one hand at room temperature. For this purpose a box was prepared and equipped with two electric lights and a thermometer. A hole was provided through which the patient inserted one hand and half of the forearm. Another hole could be opened just enough to permit an examiner to take the skin temperature. A glass window in the top provided a means of viewing the hand. The patient was exposed to room temperature (78° F.) for thirty minutes, and then basal readings recorded with the Tycos thermocouple. The absolute skin temperatures were not calculated. All readings represent only relative changes in skin temperature. The patient's left hand was fitted into the box with the palm up and resting on a square of felt. The patient, nude except for a loin cloth, then entered the refrigerator. The temperature of the refrigerator was 4° C., and that in the box was maintained at 25° C. The temperature of the finger tips of both hands was recorded at five-minute intervals. (Fig. 2). After ten minutes in the refrigerator the fingers of the right (exposed) hand blanched severely, felt quite cold, and stung with pain. The left hand, in the box, remained comfortable and of normal appearance for the twenty-minute period. At the end of this time the average temperature of the fingers of the exposed hand had fallen 14°, as compared to 5° for the left hand. The hands were then changed; the right hand was placed in the box, and, in ten minutes, the whole situation as regards temperature, appearance, and sensation was reversed.

*Experiment 2.*—The experiment outlined above was repeated, except that the temperature inside the box was maintained at 40° C. (Fig. 3). After forty minutes in the refrigerator the temperature of the fingers of the right (exposed) hand had fallen 17°, as compared to 1° for the left. The color changes and sensations were

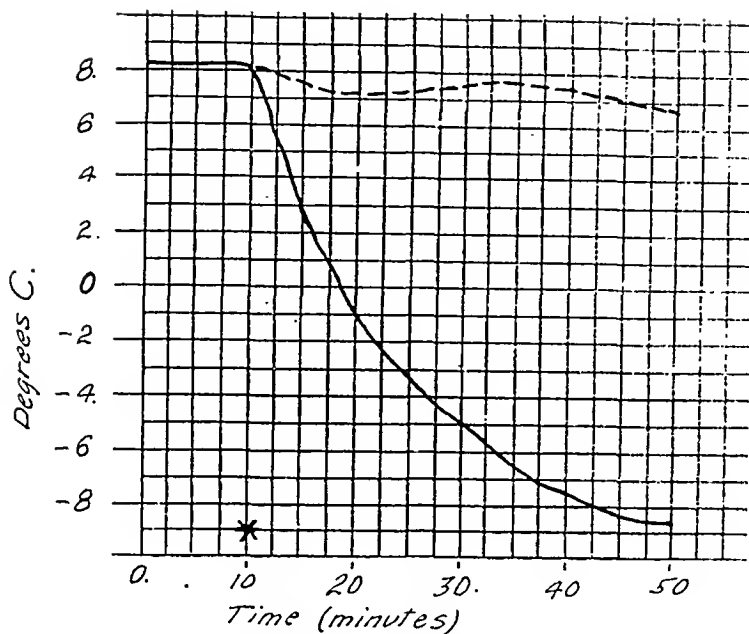


Fig. 3.—Patient E. V. was taken into a refrigerator, but his left hand was kept in a heated box. Curves represent the average skin temperature change of all fingers of each hand. Room temperature at which basal readings were taken,  $27.0^{\circ}\text{C}.$ ; refrigerator temperature,  $4.0^{\circ}\text{C}.$ ; temperature of heated box,  $40.0^{\circ}\text{C}.$ ; solid line = right (exposed) hand; broken line = left (warmed) hand. \*, Time at which refrigerator was entered.

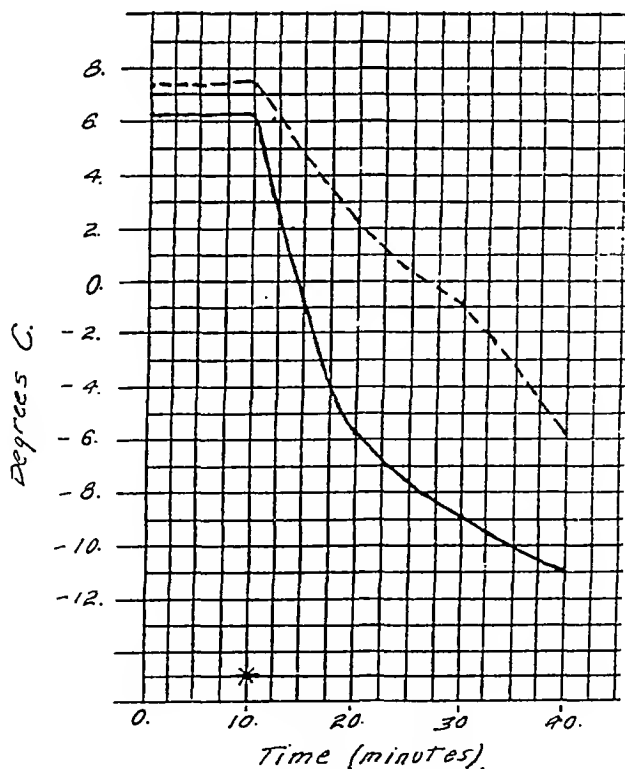


Fig. 4.—Curves showing the fall in temperature of the fingers of a nonvasospastic patient (N. B.) when the entire body was exposed in a refrigerator at  $0^{\circ}\text{C}.$  The right hand (broken line) was sympathectomized. The left hand (unbroken line) was normally innervated. Each curve represents the average of five fingers. At the end of the experiment the 5-degree difference on the two sides represents the vasoconstrictor activity of the sympathetics. The temperature readings are relative. \*, Time at which refrigerator was entered.

the same as in Experiment 1. The left hand remained quite pink, and presented a few drops of sweat. After the forty-minute period in the refrigerator the mouth temperature of the patient dropped from 98.4° F. to 97.9° F.

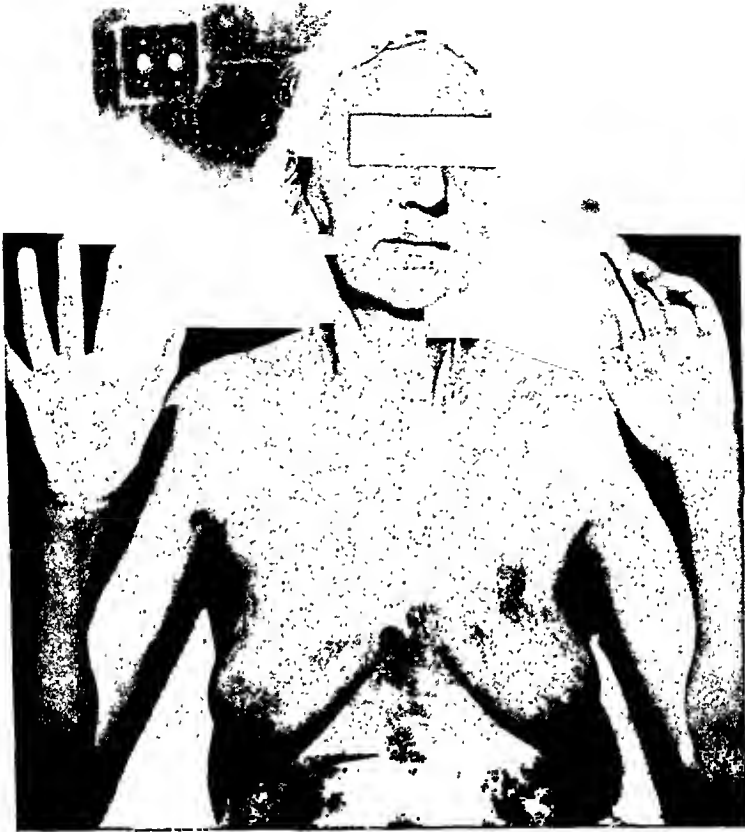


Fig. 5.—Patient E. V. Thermoregulatory sweating test, using the starch-iodine indicator of Minor. There is complete anhidrosis above the skin level of D 3 on the right, and D 2 on the left.

*Comment.*—In Experiment 1 the fall in temperature of the fingers in the warm box reflects the influence of the sympathetics on the cutaneous vessels of the fingers when the latter are kept at room temperature and the body is severely chilled. We<sup>2</sup> have studied the skin temperature of patients in the refrigerator after unilateral cervicodorsal ganglionectomy. In this case both hands were exposed. These patients did not have vasospastic disease. At the end of such an experiment the temperature on the intact side fell to a lower level than that on the sympathectomized side, and we felt that the difference was an expression of the added influence of the sympathetics on the normal side. The difference in those cases agreed roughly with the difference at the end of twenty minutes in Experiment 1. For example, a non-vasospastic patient with a unilateral dorsal sympathectomy\* was taken into the refrigerator with both hands exposed (Fig. 4). After thirty minutes the difference in temperature of the fingers on the two sides was 5° C.; the sympathectomized side was the warmer.

\*Only the second dorsal ganglion was removed on the right. The thermoregulatory sweating test and the capillary vasodilatation test<sup>1</sup> proved that this was as complete a sympathectomy of the face and upper extremity (as far as central connections are concerned) as that which results from the removal of the inferior cervical and upper two dorsal ganglia.



Experiment 2 demonstrates that an environmental temperature of  $40^{\circ}$  C. about the hand can cancel any influence that central impulses through the sympathetics may tend to have, even when the body temperature is forced down  $0.5^{\circ}$  C. If the sympathetics played the major role in causing the abnormal vasospastic state, one would certainly expect it to be manifested to a greater extent than was demonstrated in these experiments.

On Aug. 19, 1940, a bilateral sympathectomy was performed by the dorsal extra-pleural approach, as follows: *On the right*, segments of the second, third, and fourth ribs were removed. The sympathetic chain was severed below the third dorsal ganglion. All rami entering and leaving the second and third dorsal ganglia were severed. The cut end of this proximal segment of the chain was sutured to the nearest muscle. Rami to the inferior cervical and first dorsal ganglia were not molested. *On the left*, after removing segments of the first, second, and third ribs, the inferior cervical and upper two dorsal ganglia were removed. The patient therefore had, on the right, a preganglionic, and, on the left, a postganglionic sympathectomy. The sympathectomy was complete on both sides in so far as central connections were concerned, as indicated by a thermoregulatory sweating test\* (Fig. 5). The right upper extremity was perfectly comfortable after the operation, but the left ached, burned, and was sore and tender for two or three months. The syndrome closely resembled peripheral neuritis, and has been of common occurrence in our experience, as well as in that of Brown and Adson,<sup>5</sup> after cervicodorsal ganglionectomy. We believe that it can be attributed to trauma to the cords of the brachial plexus incident to removal of the stellate ganglion.

The blanching of the fingers caused by exposure to cold or immersion in ice water was not abolished by sympathectomy on either side, and it was repeatedly observed and produced at will. The patient stated, however, that the blanching was now unaccompanied by the aching and stinging pain that she formerly experienced.

In a letter which was received seventeen months after the operation on this patient, she stated that her hands still undergo the same blanching and blue color changes when exposed to cold as they did before, but that they are now practically free from the former pain and discomfort.

CASE 3.—M. S., a white woman, 26 years of age, was admitted to the hospital Jan. 26, 1941. For the preceding three years she had noticed that her hands became blue when they were exposed to cold. Later, her feet reacted in the same manner. Two weeks before admission the tip of the right thumb became gangrenous.

*Examination.*—Physical and routine laboratory examination was essentially negative except for the cold hands and feet. The tip of the right thumb was gangrenous, and the right hand was swollen and tender.

When the hands were immersed in cold water, they would become blanched, later blue, and finally pink. They ached severely when exposed to cold. This was obviously a case of Raynaud's disease.

*Experiment 1.*—The temperature of the fingers was recorded for a period of time under basal conditions as in the previous experiments. The left hand was then fitted into the warm box, as described under Case 2, and the patient taken into the refrigerator. The box was maintained at  $40^{\circ}$  C. for fifteen minutes, and then reduced to  $30^{\circ}$  for fifteen minutes. Two minutes after entering the refrigerator the right index finger began to sting and became dead white. In fifteen minutes the right hand blanched, became painful, and developed bluish islands over the

\*The starch-iodine indicator of Minor<sup>4</sup> was used.

palm and dorsal surface. Throughout the experiment the left hand, which was in the warm box, remained pink and comfortable. There was never the slightest evidence of blanching. While the temperature of the box was being maintained at  $40^{\circ}\text{C}$ . the temperature of the left hand increased. When the box temperature was reduced to  $30^{\circ}$ , the temperature of the hand fell only  $2^{\circ}$  below what it had been under basal conditions. The temperature of the tips of the fingers was recorded every five minutes. Fig. 6 shows the average temperature of the fingers of each hand. The mouth temperature was reduced  $0.5^{\circ}\text{F}$ . in thirty minutes.

*Comment.*—This experiment again demonstrates the fact that a warm environment can completely annul any tendency the sympathetics might have to produce abnormal vasospasm, even when the body is chilled sufficiently to reduce the mouth temperature by  $0.5^{\circ}\text{C}$ .

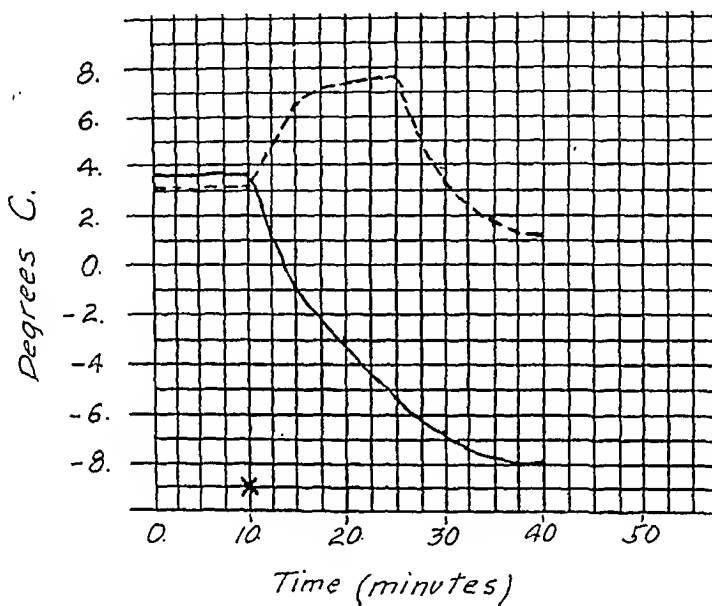


Fig. 6.—Graph illustrating the temperature changes in the fingers of M. S., Case 3. The temperatures were taken with a thermocouple, and represent only relative changes. The curves were computed from the average of the fingers of each hand. The broken line represents the values for the left hand, which was kept in a warm box. From ten to twenty-five minutes on the graph the temperature of the box was  $40^{\circ}\text{C}$ . Thereafter, it was maintained at  $30^{\circ}\text{C}$ . The unbroken line represents the values for the right hand, which was exposed to refrigerator temperature ( $5^{\circ}\text{C}$ ). Basal readings were taken at room temperature ( $78^{\circ}\text{F}$ ). \*, Time at which refrigerator was entered.

*Operation.*—On Feb. 4, 1941, an upper dorsal sympathectomy was performed on both sides, as follows: *On the right*, all rami to the second and third dorsal ganglia were severed. The chain was severed below the third ganglion and the cut end sutured to the overlying muscles. The rami to the inferior cervical and first dorsal ganglia were not molested. *On the left*, only the second dorsal ganglion was removed.

*Result in Respect to Completeness of Sympathectomy.*—The thermoregulatory sweating test, which was performed several times, indicated that, in so far as central connections are concerned, the sympathectomy was as complete on both sides as is the case after cervicodorsal ganglionectomy (removal of the inferior cervical and upper two dorsal ganglia). On the right, the level of anhidrosis was one segment lower than on the left. This case constitutes further proof that it is necessary to remove only the second dorsal ganglion to obtain complete sympathectomy of the

face and upper extremity. This case, with photographs, will be presented in another report, along with evidence that supports this statement.

*Result in Respect to the Vasomotor Abnormality.*—The hands became several degrees warmer and considerably more comfortable. The swelling of the right hand subsided in four days, but it was subsequently necessary to amputate the right thumb.

Both before and after time for degeneration had been allowed, the color changes could be invoked by immersing the patient's hands in cold water, although she stated that the aching pain formerly associated with exposure to cold was greatly relieved. No differences could be discerned in the two hands as a result of the different types of sympathectomy. The result has remained satisfactory and beneficial to the patient up to the time of writing (nine months).

#### THE MECHANISM OF RAYNAUD'S DISEASE

Raynaud,<sup>6-8</sup> in 1862, presented a classical description of the disease that has since borne his name. Raynaud regarded the disease as primarily a disorder of the sympathetic nervous system, and thought that the lesion or locus operandi was situated in the lateral grey matter of the spinal cord.

This concept was accepted practically without exception until Lewis<sup>9</sup> presented evidence to show that the cause or locus operandi of the disease was local, in the vessel itself, and did not involve primarily the sympathetic nervous system. In spite of Lewis' work, writers have generally continued to agree with Raynaud's original concept, largely because of the beneficial results of sympathectomy in the treatment of the disease. Kerr,<sup>10</sup> however, in 1930, further supported Lewis' concept. Also, Morton and Scott,<sup>11</sup> in 1931, essentially concurred with Lewis, and stated, "Thus our opinion is that Raynaud's disease is not primarily due to an abnormality in sympathetic innervation, yet that the majority of the attacks except in the most severe cases are initiated or accentuated by vasoconstrictor stimuli under the ordinary living conditions of these patients." Boggon<sup>12</sup> and Gask and Ross<sup>13</sup> concur with Lewis, but advocate sympathectomy to increase the caliber of the denervated arteries.

We shall quote Lewis' concept in his own words, and then present briefly some of the criticisms of his contention. "Local applications of heat and cold show that the spasm is profoundly influenced by temperature, in response to which the vessels behave abnormally. These observations are opposed to the current view that the spasm is vasomotor in origin; the abnormal element in the reaction to cold is a direct reaction and due to a peculiar condition of the vessel wall locally; it is not the result of a reflex through the vasomotor nerves. The state of the vasomotor nerves naturally influences the tone of the vessels in these patients as it does in normal people, but the pathological element in the vascular spasm is not of nervous origin, as at present it is generally thought to be."

We feel that Lewis has pointed out a very significant phenomenon which discredits the idea that the vasospasm is the result of a sympa-

thetic reflex mechanism. He has shown that, when the finger of a patient with Raynaud's disease is immersed in cold water, the vasoconstrictor response is limited to the part immersed. Conversely, when a finger is immersed in warm water the release of spasm is local. Evidence has been obtained to show that when one leg of a spinal monkey is immersed in ice water, the temperature of the opposite foot will fall.<sup>14</sup> The magnitude of the fall is about  $3^{\circ}$  after approximately twenty minutes. Also, it has been shown in normal man that when an extremity is warmed, other skin areas will exhibit a rise in temperature.<sup>15</sup> This latter response has been attributed to the integrated action of the hypothalamus, which is, in turn, stimulated by changes in blood temperature. Hence it is known that reflex vasoconstriction can occur by means of reflexes through the spinal cord,\* and also that vasodilatation can occur as a result of warming the hypothalamus. However, such reflexes are widespread and not limited to small areas of skin. It would require a great stretch of the imagination, in the light of what is known about the reaction of the sympathetic system, to attribute Lewis' results to anything but local vasoconstriction.

Lewis<sup>16</sup> studied six cases of Raynaud's disease after preganglionic sympathectomy. Discoloration of the fingers occurred spontaneously, or was induced, within a few days after operation in three cases. In two of the remaining three cases abnormal reactions to cold were produced with difficulty before operation but easily after operation. He expressed the belief that preganglionic sympathectomy did not restore the condition of the fingers to normal, for there was still a local abnormality similar to that which existed before operation.

White<sup>17</sup> states that the above observations of Lewis are well taken, but criticizes his interpretation of results because many of his subjects had incomplete sympathectomies, and because he studied advanced stages of the disease and did not explain an often concomitant abnormal activity of the sweat glands in Raynaud's disease.

Simpson, Brown, and Adson,<sup>18</sup> in their study of cases of mild Raynaud's disease, could not reproduce the color changes after local anesthesia of fingers or after sympathectomy, except in one case in which cervicodorsal sympathectomy was done. By wrapping the normally innervated hand in a blanket and exposing the body to cold, they produced the bluish color change in two cases. They agree that the local abnormality may be demonstrated after sympathectomy in cases of advanced Raynaud's disease.

Livingston<sup>19</sup> disagrees with Lewis' concept for much the same reasons as those given by White, but encounters the usual difficulty in ex-

\*For convenience we like to designate the local responses to stimuli as *first order responses*, those through cord reflexes as *second order*, and those through the hypothalamus as *third order*.

plaining recurrences of the disease, particularly in the upper extremity. He attributes early recurrences to an incomplete operation, or to the fact that the disease may have been too far advanced, with secondary organic changes. He ascribes late recurrences not to regeneration, which he believes is improbable, if not impossible, after ganglionectomy, but also to incompleteness of sympathectomy. He goes so far as to say that, since removal of the inferior cervical and upper two dorsal ganglia does not always cure Raynaud's disease, this operation does not eliminate all vasomotor fibers to the upper extremity.

Simpson, Brown, and Adson<sup>20</sup> favor the view that Raynaud's disease is a disease of the sympathetics, and not a local vascular disease. They admit, however, that, when it is advanced, as Lewis pointed out, sympathectomy only modifies, and does not abolish, the vasoconstrictor response to cold. They also admit that, when it is severe, there is an abnormal response of the arterioles, but they attribute this to secondary changes that have occurred in the arteries and arterioles. In the discussion of their paper, Brown states, "In this connection it is interesting to recall that hypertension was once thought to be due to structural changes in the arteries. Sir Clifford Allbutt presented convincing evidence that the increase in blood pressure preceded the organic changes. The etiologic mechanism was determined by observation and study of the early, not of the late cases of hypertension."

We feel that this analogy to hypertension stands more in disfavor of the contention of Simpson, Brown, and Adson than in its favor, because the facts concerning essential hypertension are rapidly demonstrating that the peripheral arteriole can, and does, maintain a state of functional hypertonicity exclusive of its autonomic innervation.

Learmonth,<sup>21</sup> in referring to autonomy after sympathectomy, states that it is greater in some systems (alimentary) than in others (peripheral vascular), and that it is certain that interruption of vasoconstrictor and sudomotor pathways cannot be compensated for by intrinsic nerve mechanisms. Although the arteriole may be devoid of an intrinsic nerve mechanism, it is by no means devoid of automaticity after denervation.\* The arteriole continues to respond myogenically (?) to chemical and thermal stimuli, and we<sup>1, 2</sup> have shown that when it is exposed directly to temperature changes the magnitude of the response is great.

Adson<sup>22</sup> contends that Raynaud's is a sympathetic disease because of the psychic influence on the changes in color and because the attacks may occur in a warm environment. He points out that high fever (elevation of 3 to 4° C.) abolishes the psychic influence and the cycle of color changes (attacks). He reported four interesting things after

\*It is known that the capillaries of the skin manifest an "intrinsic" nerve mechanism through the axon reflex after sympathetic denervation. It is not known whether the arterioles may be governed by a similar mechanism.

sympathectomy: (1) There is no characteristic color change during exposure to cold; (2) attacks do not occur when the patient is excited or under emotional stress; (3) there is relief of local pain and disappearance of trophic changes; and (4) the retinal arteries are actually increased in diameter.

With regard to the psychic influence on the attacks, an important consideration arises. Although we believe that Raynaud's disease is caused primarily by an abnormality of the vascular system, we can see no valid reason why, in this disease, the skin arteriole is not more responsive or sensitive to sympathetic impulses than the normal vessel. If the arteriole in cases of Raynaud's disease is abnormally sensitive to cold, it is not unlikely that it would also be abnormally sensitive to otherwise normal sympathetic impulses. This in no way implies that Raynaud's disease is primarily a sympathetic disorder. The facts are somewhat difficult to establish, but the results of our experiments, particularly those illustrated in Fig. 1, would militate against the idea that, in Raynaud's disease, the vessel is abnormally sensitive to sympathetic impulses. Likewise, it is significant that the sympathectomized vessel in Raynaud's disease is not more sensitive to adrenaline than the sympathectomized, nonvasospastic vessel.<sup>23</sup> This has also been our experience.

We are not in agreement with Adson's first observation, as given above. In connection with his second observation, it is obvious that the direct nervous pathway through which emotional factors can evoke vasomotor responses is interrupted after sympathectomy. However, the indirect mechanism by which emotion can effect vasoconstriction, through the medium of adrenaline, forms the basis of White's<sup>17</sup> explanation of the poor results with the upper extremity. With respect to Adson's third observation, we feel that the relief of pain by sympathectomy is especially important and would of itself be an indication for the operation, but the fact that the pain is relieved does not prove that Raynaud's disease is primarily a sympathetic disorder.<sup>2</sup>

Telford<sup>24</sup> subscribes to the concept that Raynaud's is a sympathetic disease and attributes the poor results after sympathectomy of the upper extremities to incompleteness of the operation.

Thus a major difference of opinion exists concerning the etiology or mechanism of Raynaud's disease. Lewis, Kerr, Morton and Scott, Boggon, and Gask and Ross, as far as we know, stand alone in their belief that it is a primary vascular disease; others have adhered to Raynaud's original contention that it is primarily a disease of the sympathetic nervous system. The cases reported here, together with studies recently completed,<sup>1, 2</sup> strengthen Lewis' contention. The belief that Raynaud's is a sympathetic nervous system disease appears to be supported largely by the fact that the disease is benefited by sympathec-

tomy.\* In the lower extremities the results are usually excellent and permanent after lumbar ganglionectomy, but in at least half the cases the results are poor in the upper extremities after cervicodorsal ganglionectomy. Although the good results after sympathectomy have promoted disagreement with Lewis, the bad results make it equally as difficult (though not admitted) to agree with Raynaud.

We believe that Lewis is correct in his contention that Raynaud's disease is primarily and essentially a local vascular disorder for the following reasons.

1. Much of the indictment of the sympathetic system rests on the fact that sympathectomy greatly benefits mild cases. The fact that it does not benefit advanced cases has led some to admit that in these there is a degree of inherently abnormal vasoconstrictor response to cold. Besides, one would not expect much benefit after organic vascular change had taken place. We can see no reason why this entire reasoning could not be changed around. If a local vasospastic disorder exists, the normally superimposed sympathetic influences (response to cold, emotion, etc.) will enhance the abnormality and use up the narrow margin of reserve possessed by the cutaneous vessels. Sympathectomy should be beneficial, and the degree of benefit will be contingent upon the severity of the disease and the magnitude of the vasoconstriction normally imposed on the vessel. Obviously, sympathectomy would give the best subjective and objective results in mild cases, but the results constitute a palliation and not a cure in the strict sense. Furthermore, if the sympathetics were at fault, the results from sympathectomy should be better even in advanced cases.

2. We have recently demonstrated<sup>2</sup> that the inherent capacity of the arterioles to respond to cold is tremendous. If, after unilateral cervicodorsal ganglionectomy, one takes the nude patient into a refrigerator at 0° C., and follows the temperature of the fingers, he will be able to measure quantitatively the magnitude of the peripheral response and that of the central response. After an hour in the refrigerator the temperature of the fingers may have dropped 10 to 18° C., and only 3 to 5° of this is accounted for by the sympathetics.

\*We are constrained to wonder how often and to just what degree the beneficial results of sympathectomy are attributed to relief of pain. We have given evidence that the aching, stinging pain incident to the early Raynaud's syndrome or to severe cold<sup>2</sup> is abolished by sympathectomy. Hence adequate cervicodorsal ganglionectomy will result in great subjective benefit, even though it may have little influence on the local progress of the disease. Our first patient, as reported in this paper, based his belief that the result was good purely upon the relief of pain. We believe that many of these afferent (sympathetic) pain-bearing fibers course in the sheaths of major vessels, and that this explains why Leriche<sup>25</sup> succeeded in abolishing the pain in his cases by periarterial sympathectomy. We feel that his evaluation of periarterial sympathectomy must be based largely on subjective relief. Of course if the disease advances to a stage where somatic pain fibers become involved by organic tissue changes, the patient may again suffer pain of a different nature.

We believe that this sympathetic pain incident to severe cold is initiated by marked vasoconstriction, but we do not believe that vasoconstriction is a *sine qua non* of sympathetic pain. It appears to be the current view that sympathetic pain implies vasoconstriction, and Morton and Scott<sup>11</sup> bring into their discussion such syndromes as amputation stump pain and causalgia as examples of the pain of angiospasm.

3. We have also observed<sup>2</sup> that the effect of cold on the normal hand (local application of ice or an induced central response) is a transient blanching, followed by dilatation of the capillaries. The sympathectomized hand in a refrigerator will exhibit very mild flushing, but nothing to compare with the flush of the normal hand. The flush of the normal hand may later develop a cyanotic hue. The purpose of this capillary dilatation, in combination with arteriolar constriction, is undoubtedly to protect the skin against the lethal effect of cold.\* When the first patient (F.C.) reported herein was exposed in the refrigerator, both hands presented islands of pallid skin and the distal two joints of all fingers were blanched. The only difference in the appearance of the two hands was one of degree. The sympathectomized hand was not quite as flushed in the nonblanched zones and not quite as cyanotic as the other hand. Although one could detect this, we doubted whether a color photograph would be able to show the difference. The sympathectomized hand felt warm subjectively and was devoid of pain, but the other hand ached and stung with cold. There was no evidence of regeneration or incomplete sympathectomy. The sweating test showed complete absence of sweating over the left upper extremity and throughout the normal distribution of the inferior cervical and upper two thoracic ganglia. The temperature of all of the fingers on the left (intact) side was significantly higher than that on the right at room temperature, except on one occasion, when the temperatures were almost the same.

Thus, in this case we witnessed a striking example of the effect of sympathectomy on the hand of a patient with Raynaud's disease. It abolished the aching, stinging pain ordinarily produced by cold, but altered the temperature and color changes only to a degree which was in keeping with what would be expected by eliminating a normal sympathetic influence.

4. We should like to call attention to the fact that cold normally causes a transient blanching, followed by flushing of the hand and

\*Capillary dilation in response to cold may be a peripheral (first order) response or a central (third order) response, and is normally a combination of the two.<sup>2</sup> After unilateral cervicodorsal ganglionectomy, a small block of ice on the forearm or hand will produce the same phenomenon and to the same degree on both the normal and sympathectomized sides. The effect is first a pallor, and this is followed shortly by reddening limited to the area of application. When the ice is removed, the flush persists for some time. This is a local (first order) reaction. If the patient is taken into a refrigerator, so that the entire body is exposed to cold, the first order reaction will be markedly re-enforced on the normal hand through the agency of central reflexes. The normal hand will become quite flushed, and later may present a cyanotic hue, whereas the sympathectomized hand will become only slightly flushed.

The flushing after local application of cold which was studied by Lewis<sup>2a</sup> is a local reaction of the first order. His supplementary studies<sup>2i</sup> involved first and third order responses. Lewis found that the reaction was not present, as is true of the histamine flare, after degeneration of peripheral nerves. The reaction was not abolished after degeneration of sympathetic nerves. Lewis therefore attributed the reaction to an axon reflex. Inasmuch as this first order response is not influenced by degeneration of sympathetic nerves, our observation in the refrigerator cannot be attributed to the latter, but constitutes strong evidence for the existence of a central control of capillary dilatation in response to severe cold. The term "central" must for the present include hypothalamic reflexes (third order response) and reflexes through the cord (second order response).



fingers, and that this capillary dilatation is an integrated response which is largely (but not entirely) under the control of central reflexes, probably through the hypothalamus. The hand of the patient with Raynaud's disease, however, becomes excessively blanched when exposed to cold and remains so for a long period of time, so that, if this blanching is a reflex vasomotor phenomenon, we can at least say that it is not in keeping with what we know the normal, integrated, sympathetic response to be. We feel justified in concluding that such observations indicate that the capillaries, as well as the arterioles, are exhibiting an abnormal, local, vasoconstrictor response to cold. This is of such a marked degree that the normally integrated central function cannot be effective in establishing capillary dilatation. The hand of the patient with Raynaud's disease will, after long exposure, go through the red and cyanotic color changes. We feel that a normal hand in the refrigerator differs from the hand of a patient with Raynaud's disease at higher temperatures only in this one respect, namely, that the capillaries of the latter exhibit a sustained constriction.\*

5. Lewis<sup>9</sup> has shown that the effects of cooling or warming a single finger of a patient with Raynaud's disease are local and that, if this is a sympathetic reflex, it does not obey the laws which characterize sympathetic reflexes.

#### SUMMARY

After digesting some of the literature and studying three cases of Raynaud's disease, we feel that the evidence is greatly in favor of the conclusion that the disease is primarily a vascular, and not a sympathetic, disorder. Sympathectomy is beneficial objectively because it eliminates the vasomotor influence which is normal in any given case. It is beneficial subjectively because it abolishes the aching and stinging pain of vasoconstriction. (Whether the relief of this type of pain is brought about by cutting afferent sympathetic fibers or by an alteration in the threshold for pain following the interruption of efferent sympathetics remains unsolved.) Our contention is based largely on the following major considerations: (1) As Lewis has shown, the vascular spasm caused by cold water and its release in warm water are strictly local phenomena. (2) We have demonstrated that, after preganglionic or postganglionic sympathectomy, the hands still retain the local disorder objectively, that is, cold continues to cause the color changes. This objective response is diminished in mild cases, but only to a degree that would be expected after eliminating the normal sympathetic vasomotor influence. (3) When a patient is taken nude into a refrigerator, and kept there long enough to cause a fall in central temperature, and, at

\*We cannot agree with Kerr<sup>10</sup> when he states that the pallor has no significance and is entirely artificial. We feel that the role of the capillaries in the vasospasm of Raynaud's disease is quite important and is probably the factor that renders the tissue liable to death.

the same time, one of his hands is kept at room temperature, the latter does not show evidence of vascular spasm, either subjectively or objectively, even though the exposed hand reacts severely. One is justified in assuming that, if the sympathetic system is responsible for the vascular spasm, the hand at room temperature under these circumstances should react somewhat like the other hand.

According to evidence which is only partly presented in this paper, preganglionic sympathectomy in itself does not provide a solution to the problem of the treatment of Raynaud's disease of the upper extremity. After preganglionic sympathectomy the upper extremity is much more comfortable than after cervicodorsal sympathectomy, but the difference is probably the result of trauma incident to removal of the stellate ganglion. We feel that the sympathectomy should be accomplished with a minimum of surgical interference and believe that it is necessary to remove only the second dorsal ganglion in order to completely sympathectomize the upper extremity. Additional data relevant to this point will be presented in another paper.

#### CONCLUSION

Raynaud's disease is a local disorder of the vascular system and not primarily a disorder of the sympathetic nervous system.

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# THE EFFECTS OF THE INGESTION OF EXCESSIVE AMOUNTS OF SODIUM CHLORIDE AND WATER ON PATIENTS WITH HEART DISEASE

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IT IS generally assumed that a restricted intake of salt and water in cases of heart failure is desirable, which implies that unlimited use of salt and water is undesirable. The basis for such an assumption, however, rests largely on theoretical considerations. It was for the purpose of gathering data regarding the effects of increase of salt and water intake on patients with heart disease that this study was undertaken. The effects of increased salt intake and increased ingestion of water were studied separately.

## PROCEDURE

Five patients, four of whom had recently recovered from heart failure, were given increased amounts of sodium chloride by mouth. The subjects were first observed while they were on a standard diet which yielded 2,000 calories and contained 62 to 75 Gm. of protein, 250 Gm. of carbohydrate, 80 Gm. of fat, 2,000 c.c. of fluid, and about 5 to 7 Gm. of sodium chloride. Preliminary observations on each patient were continued until a more or less constant state had been reached. This required four to twelve days in the various subjects. Immediately thereafter, in addition to the above diet, 10 to 12 Gm. of sodium chloride, in capsules, were given daily to the point of discomfort. These experimental periods, consequently, were variable, extending from four to fourteen days. Both during control and test periods, all patients were kept absolutely at rest in bed.

The effect of an increased ingestion of water was studied on three patients who had recently recovered from heart failure. (Two of these patients also served for the salt experiments.) During the control observations, the standard diet mentioned above varied in each case only as to its daily fluid content. To one patient, 1,000 c.c. of fluid were given; to a second, 1,500 c.c.; and to a third, 2,000 c.c. In the test period water was added so that the fluid intake was increased to 3,000 c.c. for all.

Of our six subjects, three had arteriosclerotic heart disease, and, when they entered the hospital, were suffering from severe congestive failure. Of these three, two had auricular fibrillation, and the third had delayed A-V conduction. The fourth patient had concretio cordis and auricular fibrillation and entered in a state of severe cardiac insufficiency. The fifth patient had a lesser degree of heart failure, associated with pulmonary fibrosis and pneumoconiosis. On admission, the sixth had rheumatic heart disease involving the mitral and aortic valves, and moderately severe failure. All of the patients except the last were men.

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In each case, daily observations before and during the administration of an increased amount of salt or water were carried out under basal conditions. Oxygen consumption was measured by the open (Tissot) method, or by the closed (Benedict-Roth) method. The respiratory rate and respiratory minute volume (average of a seven-minute period) were measured. The maximum of three attempts was recorded as the vital capacity. The heart rate was counted at the apex, and systolic and diastolic pressures, measured by auscultation, were taken three times within six minutes, and averaged. Frequent electrocardiograms were made. The cardiac area was estimated from a teleroentgenogram with a planimeter, according to the method of Levy.<sup>1</sup> The venous pressure was measured by means of a modified Moritz and Tabora method,<sup>2</sup> and the arm-to-tongue circulation time was estimated by the Decholin method, as described by Winternitz, Deutsch, and Brüll.<sup>3</sup> In addition, the weight of each patient was recorded daily. Sodium and chloride balances were ascertained by chemical analyses of the ingested food and the urine. The daily urinary output of chloride was measured by the method of Volhard and Arnold.<sup>4</sup> Determinations of urinary sodium were carried out upon aliquots from four-day periods, according to the method of Butler and Tuthill.<sup>5</sup> Samples taken from a homogenous mixture of an entire day's food were analyzed for chlorides by the above method. From aliquots of the dry, ashed material from the homogenous mixture of food, sodium was determined by the same technique. The fecal excretion of sodium and chloride was not measured. Urinary nitrogen was determined by the method of Folin and Denis.<sup>6</sup>

## RESULTS

*Salt Experiments.*—As might be expected, there were individual variations, but the case presented in detail below will serve to illustrate the type of reaction which can be anticipated under the conditions of our experiments.

Fig. 1 illustrates the daily observations on a patient with arteriosclerotic heart disease and auricular fibrillation. There was a control period of twelve days, during which the patient received the basic diet containing 121 meq. (2.8 Gm.) of sodium, and 140 meq. (5.0 Gm.) of chloride. During the next period 10 Gm. of sodium chloride were added daily to the basic diet.\* The intakes of sodium and chloride during this interval of increased salt administration were 289 meq. (6.6 Gm.) and 299 meq. (10.6 Gm.), respectively. This period had to be terminated in six days because of the alarming condition of the patient. During the next four days he received only the basic diet. At the end of this time, while he was still on the same diet, he was digitalized. Digitalis leaf in a dose of 0.6 Gm. daily was given for three days, then 0.2 Gm. daily for three days, followed by a maintenance dose of 0.1 Gm. for the remainder of the experiment. On the fifth day of digitalization, 10 Gm. of salt in capsules were again given daily, and continued for fourteen days. The intake of sodium and chloride during this final period was identical with that of the first high-salt period.

\*Because of a change in brands of food at this time, the sodium content of the basic diet was found to be 118 meq., and the chloride, 128 meq. These values hold from the end of the control period to the end of the experiment.

The heart rate, which was irregular, but averaged about 80 per minute in the initial twelve-day period, gradually increased during the first five days of high-salt intake to 90 or more. In the next twenty-four hours the heart rate rose sharply to 135 per minute. Following an

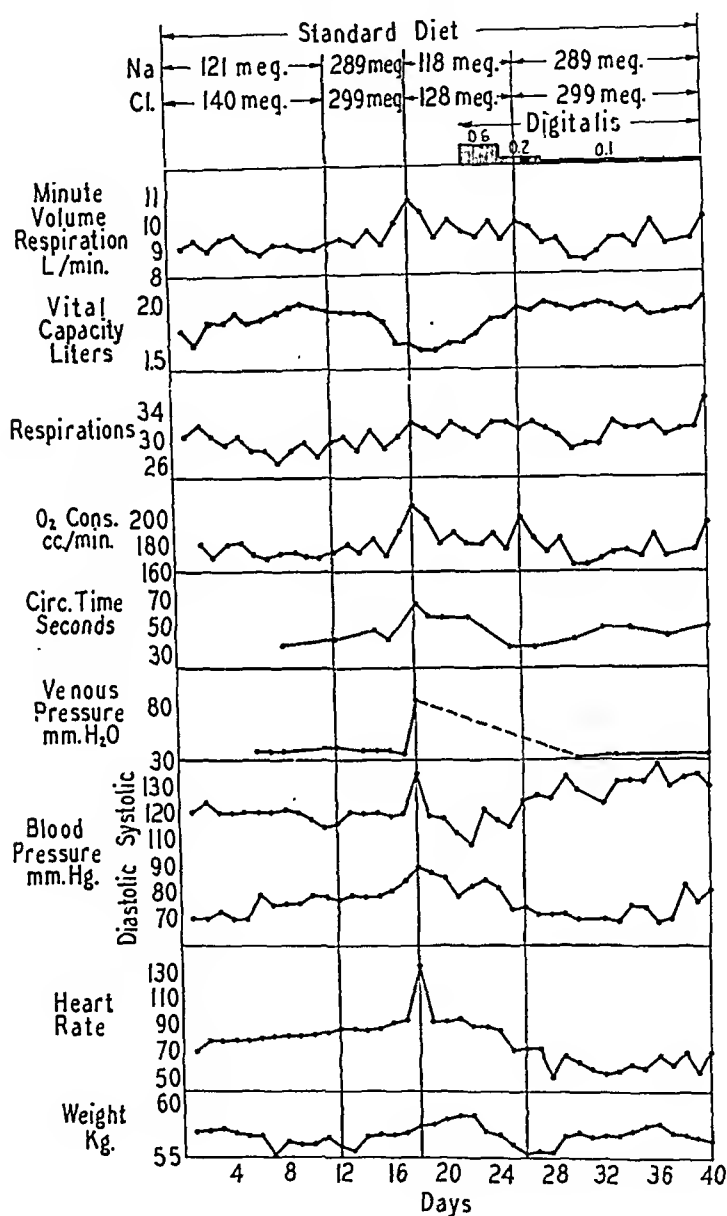


Fig. 1.

initial, rapid fall in rate after withdrawal of the excess of salt, the rate decreased gradually until digitalization was attained, when a more rapid decline set in, resulting in a fall to a level below the initial one. This improvement was maintained in spite of the second period of salt administration, although the rate showed a tendency to rise in the latter portion of this interval. In other words, there was an acute, alarming

rise in heart rate after six days of increased salt intake without digitalis, but, after the patient was digitalized, the same daily amount of salt failed to produce any marked response at the end of fourteen days.

The systolic blood pressure exhibited an acute rise of 15 mm. Hg. above the control level on the sixth day of salt administration. Immediately after withdrawal of the extra salt, the pressure fell below the initial level. However, with the administration of digitalis, the curve rose steadily in the second period of increased salt intake and reached a plateau above the control value. The diastolic pressure also increased about 15 mm. Hg at the end of the first high-salt period, but fell steadily during the administration of salt and digitalis to a level below the control value. There was, therefore, during the digitalis period, a striking increase in pulse pressure.

The venous pressure followed a course similar to that of the heart rate. During the initial control period and the first five days of the subsequent period of increased salt intake, readings of 40 mm. of water were obtained consistently. On the sixth day of the latter period a sudden rise to 90 mm. occurred. During the administration of extra salt and digitalis, however, the venous pressure remained slightly below the level of the control period.

On the sixth day of increased salt administration there was a sudden increase in the arm-to-tongue time from forty to sixty-five seconds. This tended to diminish slowly during the subsequent four days on the basic diet. With digitalization, the circulation time fell to forty seconds. In the latter part of the subsequent period of increased salt feeding and digitalis administration, the circulation time tended to rise gradually to fifty seconds.

The respiratory rate was rather irregular during the whole experiment. However, salt feeding, with or without digitalis, produced, in general, a slight rise.

During the control period the vital capacity was quite constantly between 1.8 and 1.9 L. Toward the second half of the subsequent salt period the readings fell gradually. The decline continued even after the excess salt had been withdrawn. A total decrease of 400 c.c. was observed at this time, which represents a significant change of 21 per cent. With the institution of digitalis therapy, the vital capacity returned to the initial control value, at which level it remained in spite of subsequent high-salt feeding.

The respiratory minute volume increased sharply toward the end of the first salt period to about 1.75 L. over the average control value. Withdrawal of the salt was followed by an immediate, but only partial, improvement. Digitalization produced a further improvement, but, with the administration of extra salt again in the final period, the values showed a tendency to rise.

The curve of oxygen consumption followed closely that of the respiratory minute volume. There was a marked rise during salt feeding without digitalis and improvement early in the course of digitalization, followed by a tendency to rise when increased amounts of salt were again given.

With the exception of the vital capacity, the maximal changes for all the factors observed occurred on the sixth day of the period of increased salt feeding without digitalis. This was not true of body weight. Although it increased by 1.5 kg. at this time, it continued to rise another 1.5 kg. four days after the extra salt had been withdrawn. Possibly it would have risen further, but for the administration of digitalis at this time, which resulted in a rapid loss of 4.0 kg. With the readministration of excess salt during digitalization the weight rose somewhat, but never attained the previous peak. Since the patient was in nitrogen balance during the experiment, these weight changes represented fluctuations in body water. Water balance studies from the urinary volume alone were impossible because of the appreciable but unascertainable loss by sensible and insensible perspiration.

Roentgenologic examination showed a slight increase in the size of the heart on the sixth day of excessive salt intake; the surface area increased from 174 sq. cm. to 180 sq. cm. The roentgenogram also showed some increase in the degree of pulmonary congestion and slight right-sided hydrothorax. After digitalization the heart size decreased to 158 sq. cm., the pulmonary fields appeared more radiant, and the pleural effusion receded.

Electrocardiograms showed no appreciable changes.

TABLE I  
SODIUM BALANCE DURING INCREASED SALT INTAKE

| PERIOD                          | DAYS | DAILY<br>Na+<br>INTAKE<br>(MEQ.) | AVERAGE<br>DAILY<br>URINE Na+<br>OUTPUT<br>(MEQ.) | AVERAGE<br>DAILY<br>DIF-<br>FERENCE<br>(MEQ.) | CORRECTED<br>BALANCE<br>(MEQ.) | TOTAL<br>ESTIMATED<br>BALANCE<br>(MEQ.) |
|---------------------------------|------|----------------------------------|---|---|--------------------------------|---|
| Standard                        | 12   | 121                              | 88  | + 33  | +13                            | +156                                    |
| Increased salt                  | 6    | 289                              | 182   | +107  | +87                            | +522                                    |
| Standard                        | 4    | 118                              | 151   | - 33  | -53                            | -212                                    |
| Standard and digi-<br>talis     | 4    | 118                              | 183   | - 65  | -85                            | -340                                    |
| Increased salt and<br>digitalis | 14   | 289                              | 226   | + 63  | +43                            | +602                                    |

Balance studies of sodium from measurements of the intake and urinary output revealed definite retention during periods of excess salt intake. The changes from period to period are presented in Table I. An average daily retention of 33 meq. apparently occurred during the control period. In the subsequent period of increased salt intake, the average daily retention was 107 meq. In the following four days on



the basic diet alone, an average loss of 33 meq. per day was encountered; and 65 meq. per day of sodium were excreted during four additional days on the basic diet and digitalis. A retention averaging 63 meq. per day occurred during the final fourteen days of high salt feeding and digitalis.

The course of sodium metabolism from period to period appears even more significant when the figures are corrected for the loss of sodium through other channels. Studies of insensible perspiration in normal persons show that the amount of sodium thus lost is independent of the intake and is usually close to 10 meq. per day.<sup>7, 8</sup> Furthermore, according to the literature,<sup>9</sup> as well as unpublished results obtained in our laboratories, fecal sodium, regardless of the amount ingested, is also fairly constant at 10 meq. daily.

In a group of six cases studied by us in which body weight became stationary during the control periods and the daily urinary output of sodium had reached a constant level, i.e., sodium and water equilibrium, the average difference between intake and urinary output was 22 meq. Thus, under ordinary conditions, one may consider that about 20 meq., in addition to the urinary output, represents a fair estimate of the total loss of sodium. By subtracting this amount from the observed retention, we constructed the sixth column in Table I to record "corrected sodium retention," in order to obtain a better approximation of the sodium metabolism during the course of the experiment. Thus, the total retention for the twelve-day control period was 156 meq., which is only 13 meq. per day. During the subsequent period of increased salt intake, the total retention in six days was 522 meq., or 87 meq. daily. During the following eight days on the basic diet, including four with digitalis administration, a total of 552 meq. was lost. The final salt period, with digitalis administration, revealed a retention of 602 meq. in fourteen days, or 43 meq. per day.

The total quantity of urinary chloride excretion during a four-day period was higher, as expected, than that of sodium. However, the changes of both from period to period were found to follow almost the same slopes, e.g., the degree of chloride retention closely approximated that of sodium, and need not be further elaborated.

*Water Experiment.*—Fig. 2 presents the observations in a typical experiment. The patient, a woman who had rheumatic heart disease with mitral stenosis and regurgitation and aortic regurgitation, had recently recovered from an attack of heart failure.

As a control, a standard diet containing 115 meq. (2.6 Gm.) of sodium, 135 meq. (4.9 Gm.) of chloride, and 2,000 c.c. of fluid was administered for twelve days. At the end of this time, when her condition had become stabilized, the fluid intake was increased to 3,000 c.c., but no changes were made in the diet. This amount of fluid represented an uncomfortably high intake for the patient. In other words, fluids were liter-

ally forced. This was maintained for eight days. During the next four days the fluid intake was diminished to the initial control level of 2,000 c.c.

During the first twelve days she improved, and her body weight, systolic pressure, respiratory rate, and vital capacity rapidly became stabilized. The heart rate, diastolic pressure, and basal metabolic rate decreased slightly. This trend can be fairly attributed to the bed rest.

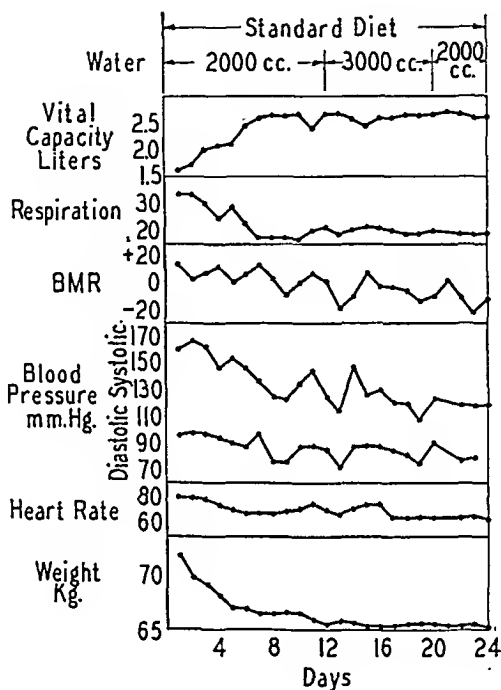


Fig. 2.

During the period of high water intake, the heart rate and basal metabolic rate tended slightly further toward normal, but everything else remained unchanged. The last four control days were likewise uneventful. The results were the same in the other two experiments, no matter whether the increase of fluid intake to 3,000 c.c. represented an additional 1,000 or 2,000 c.c. of water.

#### DISCUSSION

Increased water ingestion, as such, was apparently harmless. It should be noted that the level of salt intake in this experiment was average (2.6 Gm. of sodium, representing 6.6 Gm. of sodium chloride), and therefore this conclusion applies to a normal intake of salt. On the other hand, raising the sodium chloride intake (about 17 Gm.) produced ill effects upon the circulatory status, namely, a clinical picture which was indistinguishable from that of congestive heart failure. Comparison of the experiments with increased salt intake suggested that, in gen-

eral, the intensity of harmful effects was proportional to the degree of salt retention. This fact may account, in part, at least, for the individual variations noted.

The question arises whether the increased salt intake produced true heart failure. Actually, what is regarded as heart failure is essentially a condition in which there is an increased and more slowly circulating blood volume. It is, of course, theoretically possible that conditions other than heart failure may be accompanied by such a circulatory state. However, in view of the underlying cardiac disease and a history of previous failure, it is logical to assume that the condition we observed was, in fact, heart failure. In any event, it was indistinguishable from heart failure. In this connection it should be noted that, shortly after the turn of the century, Vaquez and Digne<sup>10</sup> were likewise impressed by bedside observations of recurrent heart failure after the administration of salt to patients whose heart disease had shown considerable improvement with rest in bed and a Karel diet (1.5 Gm. of sodium chloride).

The discussion thus far has tended to place emphasis on the effect of an increased sodium *intake* on patients with heart disease. Our results indicate that the emphasis should rather be placed on the degree of sodium *retention*, for, unless there is a significant and fairly rapid retention, no signs of heart failure appear. In other words, evidence of heart failure may be produced fairly easily by a moderate intake of sodium chloride when conditions favor sodium retention, although a great increase of sodium chloride intake may produce no ill effects when there is little or no sodium retention, as, for example, under the influence of digitalis or diuretics. The extent of salt restriction which is necessary to obviate retention in cases of heart failure is therefore variable. Since it is not practicable to ascertain this amount, and since retention must vary in the same patient from time to time, it would appear wise simply to reduce the salt intake to a minimum.

Among other factors which favor sodium retention acute infections may be mentioned. It is generally known that pneumonia causes chloride retention (and presumably sodium retention). It is not as well known that simple upper respiratory infections may likewise produce a significant degree of sodium retention. One of our patients contracted an acute upper respiratory infection in the course of an experiment, so that we had an unexpected opportunity to observe the effect upon sodium metabolism. Because such data can be obtained only by chance, and because they have a bearing upon our problem in general, we report the results in detail. Early in the control period, while the patient had moderate heart failure, there were a rapid loss of weight and a negative sodium balance, associated with nitrogen equilibrium. According to the work of Gamble, Ross, and Tisdall,<sup>17</sup> the constancy of the electrolyte concentration of body fluids allows one to approximate changes in

water balance by means of the content of base in the urine. Therefore, since 1 kg. of extracellular fluid contains 140 meq. of sodium, a loss of body weight of 1 kg., associated with a negative balance of this amount of sodium, indicates a loss of approximately 1 kg. of extracellular water. In Fig. 3 the daily cumulative changes in sodium balance and body weight are compared with each other by representing along the ordinates 1 kg. equivalent to 140 meq. of sodium. It is thus apparent that, during the first four days, at least, the loss of weight was due almost entirely to loss of extracellular fluid. On the seventh day the patient developed a sore throat and fever. Thereafter, the sodium balance studies revealed marked retention, in spite of a further slight loss of weight (Fig. 3). By the twelfth day (the nineteenth day of the experiment) after the onset of the infection, although the sodium lost initially had been entirely regained, the body weight was diminished by 4 kg. In other words, retention of sodium occurred without a concomitant gain of body water. At this time the patient was taking extra fluids. That this course of events cannot be attributed in some way to the forcing of fluids is indicated by the absence of sodium retention in the other experiments in which fluid was forced. By a similar coincidence, Maekay and Butler<sup>9</sup> also found sodium retention (daily average of 37 meq.) without concomitant water retention during an acute upper respiratory infection in a normal subject. In our case the daily average sodium balance preceding the infection was -24 meq. During the infection there was a daily average retention of 34.5 meq. of sodium.

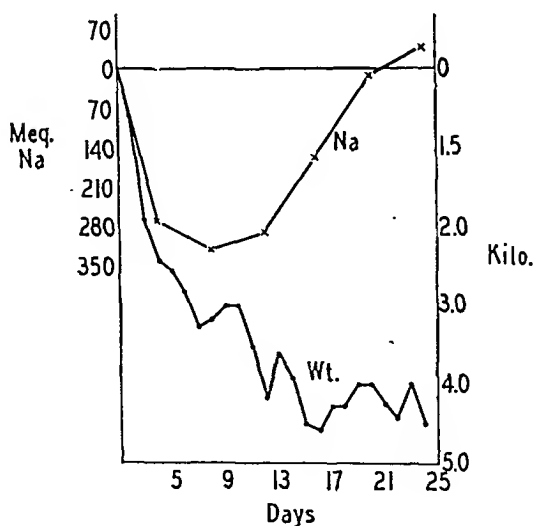


Fig. 3.

It is a common observation that the onset of heart failure in patients with heart disease is often preceded by an acute upper respiratory infection; the implication that the accompanying sodium retention may be an important precipitating factor is evident. Therefore, it seems worth

while to give a cardiac patient diuretics if he develops an upper respiratory infection. Such a procedure has appeared to be beneficial in some of our cases.

It is of interest to speculate on the mechanism involved in the relationship between sodium retention and heart failure. One possible explanation for this retention is that it results from inability of the kidneys to excrete sodium because of passive congestion. It will be recalled that in the high salt experiment, following digitalization after the initial increase in salt intake, the degree of improvement of the circulatory status was greater than in the preliminary control period. Some degree of passive congestion may therefore be postulated in our patients, who, though improved, were not fully recovered from the heart failure before the extra salt was given. With sodium retention there may be an increase of plasma volume. The consequent increase in circulating blood volume may therefore conceivably place an additional strain on an already weakened heart. This, in turn, results in greater renal congestion, thereby setting up a vicious circle. This circle can be broken either by factors which tend to strengthen the heart or decrease its work (rest, digitalis, sedatives), or act directly upon kidney function (diuretics).

Our results may be ascribed to an increase in the sodium content of the heart muscle, as suggested by Wilkins and Cullen.<sup>11</sup> These authors found from chemical analyses of normal hearts and hearts of patients who died of cardiac failure that, in the latter, the water and sodium content was elevated and the potassium content diminished. They therefore concluded that a disturbance in the relative concentrations of these electrolytes might underlie the mechanism of cardiac failure. However, proper recalculation of their results reveals that the differences in water, sodium, and potassium between the two groups could be entirely accounted for by a rise in the extracellular water content, i.e., edema fluid. Hence, since their observations could readily be explained by secondary edema of the heart muscle, it is unjustifiable to assume that the change in electrolyte content is the cause of failure of the heart muscle.

It is possible that acute and severe sodium retention may produce the clinical manifestations of heart failure even in the absence of previous heart disease. Reid and Teel<sup>12</sup> reported the appearance of acute heart failure in two patients with toxemia of pregnancy. Ferrebee, Ragan, Atehley, and Loeb<sup>13</sup> reported similar changes in patients with Addison's disease after overdoses of desoxycorticosterone, associated with an increase of plasma volume. Wilder<sup>14</sup> observed acute heart failure with a low-potassium and high-sodium diet and desoxycorticosterone. In acute nephritis, similar changes may supervene.<sup>15</sup> In these conditions, what is apparently heart failure may well be associated with acute sodium retention, leading to a rapid increase in circulatory blood volume, but without underlying cardiac weakness. However, it is quite pos-

sible that, in such cases, we are dealing not with true heart failure but with a circulatory condition clinically indistinguishable from heart failure.

As to the effect of increased water intake, there would appear to be no sound theoretical reasons why such an increase should be harmful. This is true at least of an increase in fluid intake to such an amount as patients with heart disease might spontaneously take without too great discomfort. Since the kidney offers no barrier to the excretion of water itself, and since no retention is possible without an equivalent supply of sodium and chloride, there is no reason why water could not be reasonably easily eliminated. Since there is only a transient rise, and that of small degree, in cardiac output after the ingestion of as much as 1,000 c.c. of water in a few minutes,<sup>16</sup> there is little added strain upon the heart. The ingestion of ordinary amounts of water, therefore, would be expected to be harmless.

#### SUMMARY

1. In patients who are recovering from heart failure, a moderate increase in the ingestion of sodium chloride may produce, within four to eight days, a clinical picture which is indistinguishable from that of congestive heart failure. Such an effect is obviated by digitalization.

2. Under similar conditions, an increase to 3,000 c.c. in the daily intake of water for as long as eight days results in no measurable or noticeable harmful effects.

3. The harmful effects of an increase in the intake of sodium chloride are apparently related to the degree of sodium retention, rather than the increased intake as such.

4. The possible mechanism of sodium retention is discussed.

5. It is suggested that, since there is a significant degree of sodium retention during upper respiratory infections, the latter may play a role in the oft-observed relationship between infection and the precipitation or aggravation of heart failure.

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MAUDE E. ABBOTT

1869-1940

Maude Abbott died more than a year ago, in the fall of 1940. She is still sorely missed by her many friends, and will be missed throughout the lives of those who knew her.

Here and there appeared brief tributes and biographical notes soon after her death, and a memorial meeting to her was held in October, 1940, in Boston, by the New England Heart Association. Abstracts of some of the addresses given at that meeting were published in the McGill Medical Journal in October, 1940 (Vol. X, p. 28), as was a list of Maude Abbott's books and papers on cardiovascular disease prepared by Donald Bauer. To bring the most pertinent quotations and the useful bibliography to the readers of the AMERICAN HEART JOURNAL, it has been suggested that the present note be published.

The first article of the series in the McGill Medical Journal was by Dr. Charles F. Martin, Emeritus Dean of Medicine, McGill University. His opening words were as follows:

"Doctor Maude E. Abbott was buried in the churchyard of her little native town of St. Andrews by the side of her forebears, and among the flowers and trees she loved so well—a simple, quiet burial, as if the life just ended had been like a thousand others. She was as consistently humble in the realm of the dead as in life.

"A few hours previously, at a service in Montreal, the English cathedral had been crowded by members of the faculty and the teaching staff, medical students, and hundreds of citizens who came to pay her homage, because they loved her.

"In this manner was closed the life chapter of a scholar at McGill who, with but few exceptions, had greater international repute and contacts than anyone in the Canadian profession."

The next paper, by Dr. Paul D. White, of Boston, concerned Maude Abbott's contributions to cardiology. The following paragraphs were the opening and closing ones.

"Maude Abbott's very first paper entitled 'So-Called Functional Heart Murmurs' gave evidence of her absorbing interest in cardiology from the earliest days of her medical career. This paper was published in the Montreal Medical Journal in 1899 and was based on the records of 466 patients with murmurs encountered on the wards of the Royal Victoria Hospital in the years from 1895 to 1898 while Maude Abbott served as graduate student there in clinical medicine and in pathology following her return from two years of study in Europe which in turn



followed her graduation in medicine from Bishop's College in 1894. Dr. Abbott at the outset credited Dr. Charles F. Martin with the suggestion that she undertake this study, and it is a great pleasure for those of us who have had the privilege of counting both these medical leaders as friends to learn that the life-long collaboration between them was so evident in these early days.

"This interesting and useful paper on 'So-Called Functional Heart Murmurs' is worth reading today. Dr. Abbott pointed out that 'functional' pulmonary and mitral systolic murmurs are common in anemia, fevers, and certain toxic states, and that even diastolic murmurs may not have an organic origin in the fashion of deformity of the valves themselves.

"During the next year, 1900, in the Philadelphia Medical Journal, doubtless as the result of Sir William Osler's advice, Maude Abbott published a note on a specimen showing a small saccular aneurysm and an accessory branch of the right renal artery. At this time Maude Abbott was reviewing and cataloguing Sir William's museum specimens left at McGill and came across a unique case of malformation of the heart described originally by A. F. Holmes in the Transactions of the Edinburgh Medico-Chirurgical Society for 1824. Maude Abbott republished this article in the Montreal Medical Journal in 1901 and this case along with others with congenital defects of the heart laid the foundation of her interest in congenital heart disease which steadily mounted from that time on under the stimulus of Sir William Osler with whom she frequently conferred. Being aware of her experience in this subject and believing that she was already a leader and perhaps the leader on this side of the water in this field, Sir William asked her to write the section on congenital cardiac disease in his *System of Modern Medicine, Its Theory and Practice*, prepared with Thomas McCrae and published by Lea and Febiger in 1908."

"The Clinical Classification of Congenital Heart Disease in 1924 supplemented by the article in the *Lancet* in 1929 presented the very practical division that she made of patients with congenital heart disease into the acyanotic and the cyanotic groups with which the world is now familiar and which has come to be currently accepted. Perhaps this along with the final tabular analysis of 1,000 cases is Dr. Maude Abbott's chief contribution to cardiological literature.

"However, when we review Maude's Abbott's influence in the field of cardiovascular disease we find that far more important than any of her written works was her vital stimulus to others. Her spirit was indefatigable. She inspired innumerable other workers throughout the world and was always very willing, in fact eager, to place at the disposal of anyone who sought it, her own vast experience and the details of pathological and clinical findings in the cases she had studied herself or analyzed in the literature.

"Thus it may be said that many of the contributions, sometimes very important, to our knowledge of congenital heart disease made by others, are due directly to Maude Abbott's influence. What little has been accomplished in the field of congenital heart disease by our own group at the Massachusetts General Hospital can be traced in major part to our acquaintanceship with Maude Abbott. She was an inspiration to us all, pathologists and clinicians alike. Her presence acted as a ferment and yet the most pleasant sort of a ferment. She often started controversies, but there was never anything that was disagreeable about any of them, for her personality, generosity, and friendship were of the very highest type. Cardiologicial literature will miss her, but the living medical world as such will miss her still more. Thus, it is not simply as the world's authority on congenital heart disease that Maude Abbott will be missed and best remembered but as a living force in the medicine of her generation. Hers was a great spirit."

Then came the paper by William Boyd, of Toronto, on Maude Abbott and medical museums. It began as follows:

"It is difficult for anyone connected with the International Association of Medical Museums to believe that Maude Abbott is dead, or to picture that association without the vivifying stimulus of her enthusiasm. At the very first meeting in Washington on May 15th, 1907, she was elected secretary-treasurer, a post which she held until her death, and I suspect that it was mainly due to her that the association came into being. She acted as editor of the bulletin of the association from 1907 to 1938. The international aspect of the association was particularly dear to her heart, although at times she found it none too easy to get her fellow-members on the council to share her enthusiasm. It is interesting to note that by the time of the second meeting the following officers had been elected: President: Prof. W. G. MacCallum, of Baltimore (a graduate of Toronto); First Vice-President: Prof. Sims Woodhead, of Cambridge; Second Vice-President: Prof. James Ritchie, of Edinburgh; Third Vice-President; Prof. Ludwig Aschoff, of Freiburg, Germany, whilst Prof. J. G. Adami, at that time Professor of Pathology at McGill, was on the Editorial Board of the Bulletin. The formation within recent years, entirely as the result of her efforts, of a British section of the association, was a source of special pleasure to her. Unfortunately the days of indiscriminate internationalism are gone for the present.

"The first time that I attended a meeting of the International Association of Medical Museums was over twenty years ago. It did not take me long to discover that the prime mover in the association, the mainspring of its energy, was Maude Abbott. For many years since then I have had the opportunity to observe the part which she has played in the life of the association. A meeting of the association

without 'Maude' as the central point round which everything revolved would be like witnessing the play of Hamlet without the Prince of Denmark."

Dr. W. W. Francis, Osler Librarian at McGill University, wrote of Maude Abbott—Hero-Worshiper:

"One of Maude Abbott's most precious possessions was a holograph letter which reads as follows:

13 Norham Garden,  
Oxford, Jan. 23, '08.

Dear Dr. Abbott,

I knew you would write a good article but I did not expect one of such extraordinary merit. It is by far and away the very best thing ever written on the subject in English—possibly in any language. I cannot begin to tell you how much I appreciate the care and trouble you have taken, but I know you will find it to have been worth while. For years it will be the standard work on the subject and it is articles of this sort—and there are not many of them—that *make* a system of medicine. Then too the credit which such a contribution brings to the school is very great.

Many, many thanks!

Sincerely yours,

(signed) Wm. Osler.

P.S.—I have but one regret, that Rokitansky and Peacock are not alive to see it. Your tribute to R. is splendid. My feelings were the same when I read the monograph.

"It refers, of course, to her celebrated monograph, 'Congenital Cardiac Disease' in vol. 4, 1908, of the first edition of Osler and McCrae's 'System,' more widely but less happily known on this side of the water by the ephemeral, salesmanish title, 'Modern Medicine,' on which its American publishers insisted. Such a letter, obviously sincere, was not only a laurel wreath and a passport to fame, but an incentive to even better work if possible. She was again deeply touched when we discovered, only last year, that Osler had inserted a photo of her in his own copy of that volume on the page opposite the beginning of the monograph."

Helen McCurchy, of Toronto, and Elizabeth MacKay, William C. Gibson, and Donald deF. Baner, of Montreal, ended the series of papers with tributes to Maude Abbott, especially as a teacher. Gibson's own experience was very illuminating:

"When I was a student in first year medicine here in 1933, I began a study of a set of little memo books in the Osler Library which were used by Sir William for jotting down all manner of quotations and case histories. One day a heavy, grey-haired woman came into the Library where I was working, and recognizing the Osler notebooks, asked me if I were an out-of-town researcher in medical history. I replied that I was a first year student at McGill and was interested

in Osler. That was my fatal mistake! I was at once whisked downstairs by this bustling human dynamo who seemed only to cling to the stair rail, letting her feet find the steps if they could. Within a few minutes I was in the midst of a sea of charts, books and pictures. A new edition of the Osler Bibliography was about to be born—but first, ‘some medical student with spare time’ must be found to help ‘with a few simple details.’ I was the simple medical student, and the innocent details of the Bibliography haunted my slumbers for the next five years. I walked out of her book-laden office wondering to myself, ‘What have I put my foot into now?’ What a naive idea! I was soon to be utterly immersed in the sea of Osler’s myriad publications, ranging from tapeworms to nurses’ education. We would have bouts of activity periodically, trying to classify Osler’s papers into a few large divisions such as Natural Science, Pathology, Clinical Medicine, Literary and Educational papers.

“When I went off to Oxford in 1935 I pleaded that the broad expanse of the Atlantic Ocean would make it difficult to continue work on the Bibliography. Not at all! Dr. Abbott was sure that the Oslerian atmosphere of Oxford would contribute enormously to the success of the work. So I wearily trundled several copies of an earlier bibliography over to England for the time-consuming preparation of an index to Osler’s contributions. I lived over a tea-room and appropriated 26 cream pitchers from the landlady, one for each letter of the alphabet. I cut up the old bibliographies into strips each bearing a single item, and had no sooner got most of them into their respective jugs than a new maid on the premises threw them all out. Finally, when Dr. Abbott wrote as if she might come over and scalp me as a low grade procrastinator, I set to work to paste the items for the the index on a long roll of narrow-gauge wallpaper, and after three days of nothing but glue and tea I got the enormous bundle off to Montreal.

“Never have I heard such rejoicing. ‘Maudie’ wrote ecstatically about the large consignment of wallpaper and she confided that the new Osler Bibliography was near term. It finally appeared in 1939.”

The set of contributions closes with the list of Maude Abbott’s publications on cardiovascular disease.

#### MAUDE ABBOTT’S PUBLICATIONS ON CARDIOVASCULAR DISEASE

1. On so-called functional heart murmurs.  
Montreal Med. J. 1899, 28:1-13  
Read by Dr. James Stewart to Montreal Medico-Chirurgical Society November 21, 1898, leading to Dr. Abbott’s election as the first woman member.
2. Note on specimen showing a small saccular aneurysm on an accessory branch of the right renal artery.  
Philadelphia M. J. 1900, 6:959-60

3. Museum notes (report of a case published by A. F. Holmes in the Trans. Edinburgh Med.-Chi. Soc., 1824).  
Montreal Med. J. 1901, 30:522-33; also: R. C. Kirkpatrick, Montreal, 1901, 11p. 4 pl.  
Three-chambered heart identified by Osler as that presented to the Edinburgh group by the first Dean of the McGill Medical Faculty.\*
4. Congenital Cardiac Disease.  
in: Modern Medicine (Osler & McCrae)  
Lea & Febiger, Phila. & New York, 1908, 4:323-425  
2nd edition, 1915, 4:323-448  
3rd edition, 1927, 4:612-821  
Of which article Osler wrote: "I knew you would write a good article but I did not expect one of such extraordinary merit. It is by far and away the very best thing ever written on the subject in English—possibly in any language."
5. Statistics of congenital cardiac disease (400 cases analyzed).  
J. Med. Research, 1908, 19:77-81  
Herein was begun Dr. Abbott's celebrated "chart." Cf. items: 4, 6, 39.
6. A chart for the study of congenital cardiac disease.  
Montreal Med. J., 1908, 37:170-3
7. Report of an unusual case of congenital cardiac disease, defect of the upper part of the interauricular septum (persistent ostium secundum), with, for comparison, a report of a case of persistent ostium primum.  
(with Joseph Kaufmann, M.D.)  
J. Path. & Bact., Cambridge, 1910, 14:525-35
8. Patent ductus arteriosus with acute infective pulmonary endarteritis.  
(with W. F. Hamilton, M.D.)  
Tr. Ass. Am. Physicians, 1914, 29:294-308  
Summary of 10 other cases from the literature is included.
9. Reversed torsion of the human heart.  
(with F. T. Lewis, M.D.)  
Anat. Record, 1915, 9:103-5
10. Congenital pulmonary atresia with perforate interventricular septum in a patient aged nine years and six weeks.  
(with S. B. Wolbach)  
Internat. A. M. Museums Bull., 1915, 5:125-9
11. Two cases of widely patent foramen ovale.  
Ibid., 1915, 5:129-34  
Specimens and lantern slides shown to Montreal Medico-Chirurgical Society and the discussion which followed was printed in: C.M.A.J. for October, 1915.
12. On the differentiation of two forms of congenital dextrocardia.  
(with J. C. Meakins, M.D.)  
Ibid., 1915, 5:134-8
13. Double monster of janus type: cephalothoracopagus monosymmetros cyclops synotus.  
(with Joseph Kaufmann, M.D.)  
Ibid., 1916, 6:95-101
14. Reversed torsion of the ventricular bend of the embryonic heart in the explanation of certain forms of cardiac anomaly.  
(with F. T. Lewis, M.D.)  
Ibid., 1916, 6:111-15

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\*The Osler Memorial Number of the C. M. A. J., 1920, 10: 91-102 "The Pathological Collections of the late Sir William Osler."—Maude Abbott.

15. On the difference between the carbon-dioxide tension in the arterial and venous blood as a diagnostic sign in cardiac septal defects.  
(with Walter M. Boothby, M.D.)  
*Ibid.*, 1916, 6:122-6
14. Foetus holoacardius acornus in heterologous (triplet) pregnancy.  
(with G. W. Phelan, M.D.)  
*Ibid.*, 1916, 6:107-11
17. The irritable heart of soldiers and the Hampstead heart hospital.  
*Ibid.*, 1918, 7:166-74  
The editorial note by A. S. Warthin and the bibliography are noteworthy.
18. Clinical and developmental study of a case of ruptured aneurysm of the right anterior aortic sinus of Valsalva, leading to a communication between the aorta and the base of the right ventricle, diagnosed during life.  
Contributions to Medical and Biological Research (dedicated to Sir William Osler, in honour of his seventieth birthday, July 12, 1919, by his pupils and his co-workers).  
Paul Hoeber, New York, 1919, 2:899-915
19. Rare cardiac anomaly: cor triloculare biventriculare in mirror-picture dextrocardia with persistent omphalo-mesenteric bay, right aortic arch and pulmonary artery forming descending aorta.  
(with Bret Ratner, M.D., and W. W. Beattie, M.D.)  
*Am. J. Dis. Child.*, 1921, 22:508-15
20. Parasitic thoracopagus with cardiac anomaly in the host (cor biatriatum triloculare, transposition of arterial trunks and patent ductus arteriosus).  
(with W. F. Watton, M.D.)  
*Internat. A. M. Museums Bull.*, 1922, 8:165-76
21. Cardiac defects in the light of the comparative anatomy of the vertebrate heart.  
(with Eleanor Shanly, M.Sc.)  
*Ibid.*, 1922, 8:188-213
22. Differential study of a case of pulmonary stenosis of inflammatory origin (ventricular septum closed) and two cases of (a) pulmonary stenosis and (b) pulmonary atresia of developmental origin with associated septal defect and death from paradoxical cerebral embolism.  
(with D. S. Lewis, M.D., and W. W. Beattie, M.D.)  
*Am. J. Med. Sc.*, 1923, 165:636-59  
With an historical summary of paradoxical cerebral embolism.
23. Cyanosis (review of an article by C. Lundsgaard and D. Van Slyke in: *Medicine*, 1923, 2:1-76).  
*C. M. A. J.*, 1923, 8:601-4  
The Van Slyke technique is hailed as an epoch-making achievement paralleling in physiology the pathological contributions to congenital heart disease of Rokitsansky.
24. Treatment of congenital cardiac disease.  
in: Blumer-Billings-Forscheimer System of Therapeutics, 3rd. ed.  
Appleton & Co., New York, 1924, 4:322-62
25. New accessions in cardiac anomalies. I—Pulmonary atresia of inflammatory origin. II—Persistent ostium primum with mongolian idiocy.  
*Internat. A. M. Museums Bull.*, 1924, 10:111-16
26. The clinical classification of congenital cardiac disease.  
(with W. T. Dawson, M.A.)  
*Internat. Clin.*, 1924, 4:155-88  
also: 75th Anniversary Volume of the Women's Medical College of Pennsylvania, 1925, pp. 11-56

27. On the incidence of bacterial inflammatory processes in cardiovascular defects and on malformed semilunar cusps.  
Ann. Clin. Med., 1925, 4:189-218  
Conclusions based on analysis of "a total of 680 cases charted to date."
28. Multiple associated anomalies.  
(with M. Lichtenwald-Myers, M.D., and Margaret Dalsell, M.D.)  
Proc. Path. Soc. of Phila., 1925, 27:22
29. The diagnosis of congenital cardiac disease.  
in: Blumer's Bedside Diagnosis  
W. B. Saunders Co., Philadelphia, 1928, 2:353-514
30. Coarctation of the aorta of the adult type: complete obliteration of the descending arch at insertion of the ductus in a boy of fourteen.  
(with W. F. Hamilton, M.D.)  
Am. Heart J., 1928, 3:381-421
31. Coarctation of the aorta of the adult type: statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years.  
Ibid., 1928, 3:574-618  
Noteworthy bibliography of 255 items.
32. Double aortic arch and pulmonary atresia, with pulmonic circulation maintained through persistent left aortic root, in a man aged 29.  
(with Digby Wheeler, M.D.)  
C. M. A. J., 1928, 19:297-303
33. Interventricular septal defect with dextroposition of aorta and dilatation of the pulmonary artery terminating by cerebral abscess.  
(with E. A. Baumgartner, M.D.)  
Am. J. Med. Sc., 1929, 177:639-47
34. Mirror-picture dextrocardia, complicated by mitral aplasia and pulmonary hypoplasia, with great hypertrophy of the transposed "right" chambers.  
(with W. Moffatt, M.D.)  
C. M. A. J., 1929, 20:611-16
35. Bicuspid aortic valve of congenital origin with associated defect of the interventricular septum and streptococcal endocarditis with mycotic aneurysm of left coronary artery and extensive recent infarction of myocardium of left ventricle.  
(Abstract.)  
(with W. H. Chase, M.D.)  
J. of Tech. Methods (formerly the Internat. A. M. Museums Bull.) 1929, 12:171-4
36. On the clinical classification of congenital cardiac disease.  
Lancet, 1929, 2:164-7  
Abridged from an address at the New Sussex Hospital, Brighton, England
37. On the relative incidence and clinical significance of a congenitally bicuspid aortic valve. With five illustrative cases.  
in: Emanuel Libman Anniversary Volumes  
International Press, New York, 1932, 1:1-38  
Including 129 references and noteworthy illustrations.
38. The McGill University Exhibit. Development of the heart and the clinical classification of congenital cardiac disease.  
British Med. J., 1932, 2:1197-9  
The exhibit was originally presented in New York City at the Academy of Medicine, 1931. This description pertains to the presentation in London on the occasion of the Centenary of the British Medical Association. A huge copy of Dr. Abbott's "chart" of 1,000 cases of congenital heart disease was included.

39. Congenital heart disease.  
in: Nelson's Loose Leaf Medicine  
Thomas Nelson & Sons, New York, 1932, 4:207-321  
The "chart" appears in its final form: an analysis of 1,000 cases.
40. Stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum. With two illustrative cases.  
(with W. W. Eakin, M.D.)  
Am. J. Med. Sc., 1933, 186:860-70
41. Clinical lecture on the differential diagnosis of congenital cardiac disease.  
Internat. Clin., 1934, 3:15-45  
Delivered as a theater clinic at the Montreal General Hospital for the Seventeenth Meeting of the American College of Physicians.
42. Congenital cardiac abnormalities.  
in: The Cyclopedia of Medicine (Piersol)  
F. A. Davis Co., Philadelphia, 1935, 3:225-41  
1939, 3:605-20
43. Diseases of the Heart.  
by John Cowan, M.D., and W. T. Ritchie, M.D. (book review)  
C. M. A. J., 1935, 33:234
44. Atlas of Congenital Cardiac Disease.  
American Heart Association, New York, 1936, 62 pp., 25 plates.  
247 illustrations.  
Here is the McGill University Exhibit (cf. item 38) in permanent form.
45. The clinical aspects of congenital cardiac disease.  
in: Modern Concepts of Cardiovascular Disease  
American Heart Association, New York, 1936, Vol. 5, nos. 3 & 4
46. A differential study on the congenital or acquired origin of bicuspid aortic valves (editorial).  
J. of Tech. Methods, 1936, 15:5-6
47. Symposium upon the relative incidence of congenital cardiac disease.  
(General Considerations.)  
J. of Tech. Methods, 1936, 15:85-6
48. Congenital cardiac abnormalities.  
in: Diagnosis & Treatment of Cardio-Vascular Disease  
F. A. Davis Co., Philadelphia, 1940, pp. 14-41

PAUL D. WHITE.



## Department of Clinical Reports

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### POST-PARTUM COLLAPSE ASSOCIATED WITH ABNORMALITIES OF THE CARDIAC MECHANISM, WITH CONTINUOUS ELECTROCARDIOGRAPHIC STUDIES

RICHARD H. MARSHAK, M.D.

NEW YORK, N. Y.

WHEN shock occurs during labor, or immediately thereafter, it is usually due to post-partum hemorrhage, placenta previa; abruptio placentae, or rupture of the uterus. Post-partum collapse may also occur under circumstances which give rise to shock in nonpregnant women. For example, shock following labor may be caused by rupture of a heart valve, hemorrhage from a gastric ulcer, rupture of an aneurysm of the splenic artery, or hemorrhage from a subperitoneal hematoma. Sudden shock due to valvular disease has been described frequently. The case herein reported is one of collapse caused by abnormal tachycardias. We were able to obtain continuous and complete electrocardiographic studies in this case, which is sufficiently rare to warrant recording.

#### CASE REPORT

Mrs. A. F., a white woman, aged 34 years, was admitted Jan. 19, 1940, in active labor.

*Past History.*—The patient had aches and pains in her legs as a child, but at no time were her joints red, swollen, or tender. The family was informed that she had a cardiac impairment, and consequently they had sent her to a special school for children with heart trouble. She had suffered from fatigability and dyspnea on slight exertion as long as she could remember but had apparently never had cardiac failure. On admission, she had moderate dyspnea on slight exertion and was somewhat orthopneic. No edema, nocturia, or other cardiac symptoms were noted.

*Obstetrical History.*—In 1932 the patient gave birth to a 6-pound girl after a labor of eighteen hours. The puerperium was uneventful. Her last menstrual period occurred April 11, 1939, and her expected date of delivery was Jan. 18, 1940.

*Physical Examination* (on admission).—The patient was well developed and well nourished. Her pulse was regular and of good quality and averaged 100 beats per minute. There was considerable posterior nasal discharge, and the posterior pharyngeal wall was slightly injected. The pupils reacted to light and accommodation normally. The lungs were normal. The apical impulse of the heart was in the fifth intercostal space at the left midclavicular line, and the heart sounds were of good quality. No murmurs were audible.

*Abdominal Examination.*—The fundus was at the level of the ensiform process. The back of the fetus was easily palpable on the right, and the small parts were

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From the obstetrical service of Dr. Harry Aranow, Morrisania City Hospital.  
Received for publication Oct. 9, 1940.

not felt. The fetal heart rate was 140 per minute, and the heart sounds were most easily heard in the midline. The head was unengaged and could be felt distinctly above the symphysis. Rectal examination revealed one-finger dilatation, with a moderately thick cervix. On admission the blood pressure was 105/70, and the temperature, 98.6° F. Labor pains were occurring every fifteen minutes. Ten

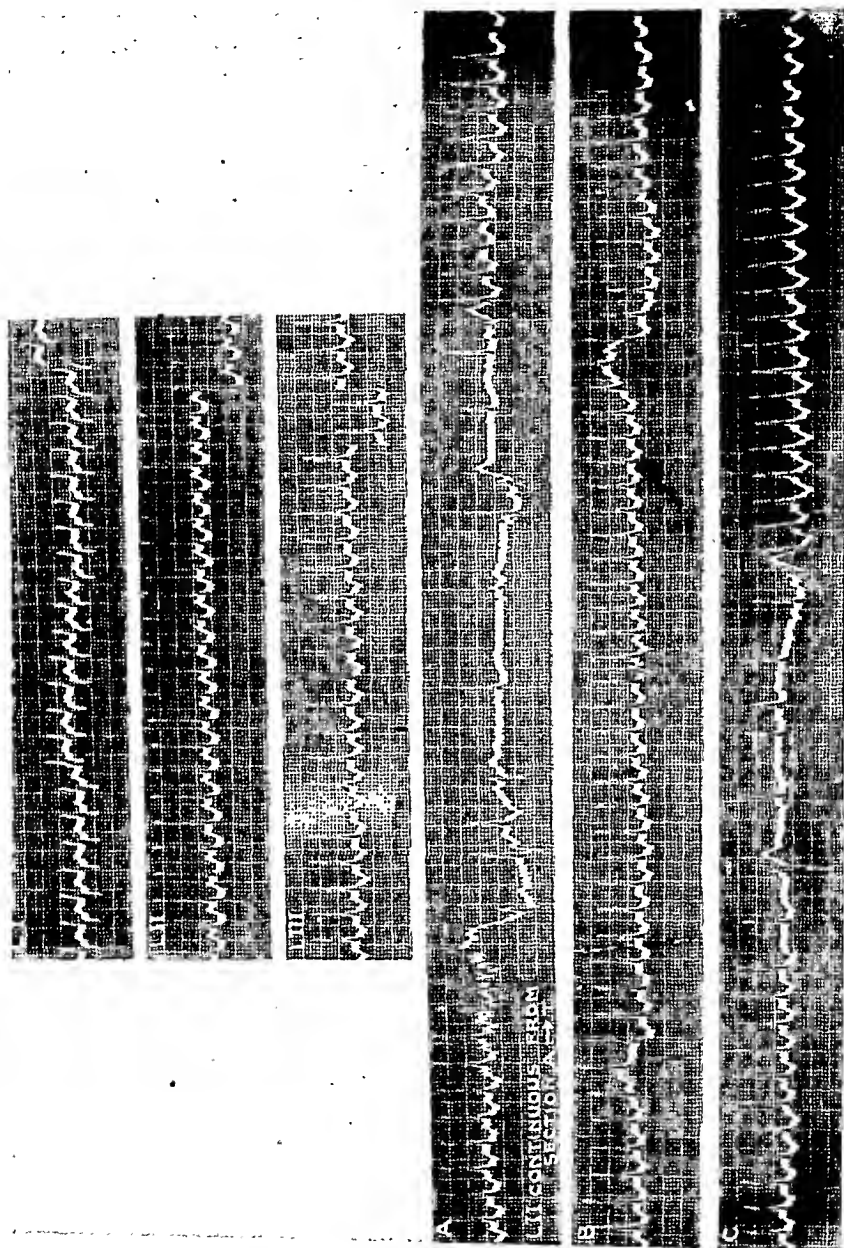


Fig. 1.

hours later the cervix was fully dilated and the head was on the perineum. The head remained on the perineum for one hour, at which time, because of her cardiac history, a low, prophylactic, forceps extraction was done. The small episiotomy was repaired. The placenta and membranes were expelled intact, and there was a slight amount of bleeding. Ether anesthesia was used. Ten minutes after delivery the patient became slightly cyanotic, and the pulse rate became so rapid that it could not be counted.

An electrocardiogram was taken immediately, for an abnormal tachycardia was evidently present. Leads I, II, and III showed a nodal tachycardia, with a rate of 215 per minute. The machine was allowed to run, and eyeball pressure was applied. The effects of this are graphically shown in the middle section of Lead II *A*. There was a recurrence of regular sinus rhythm, with extrasystoles and

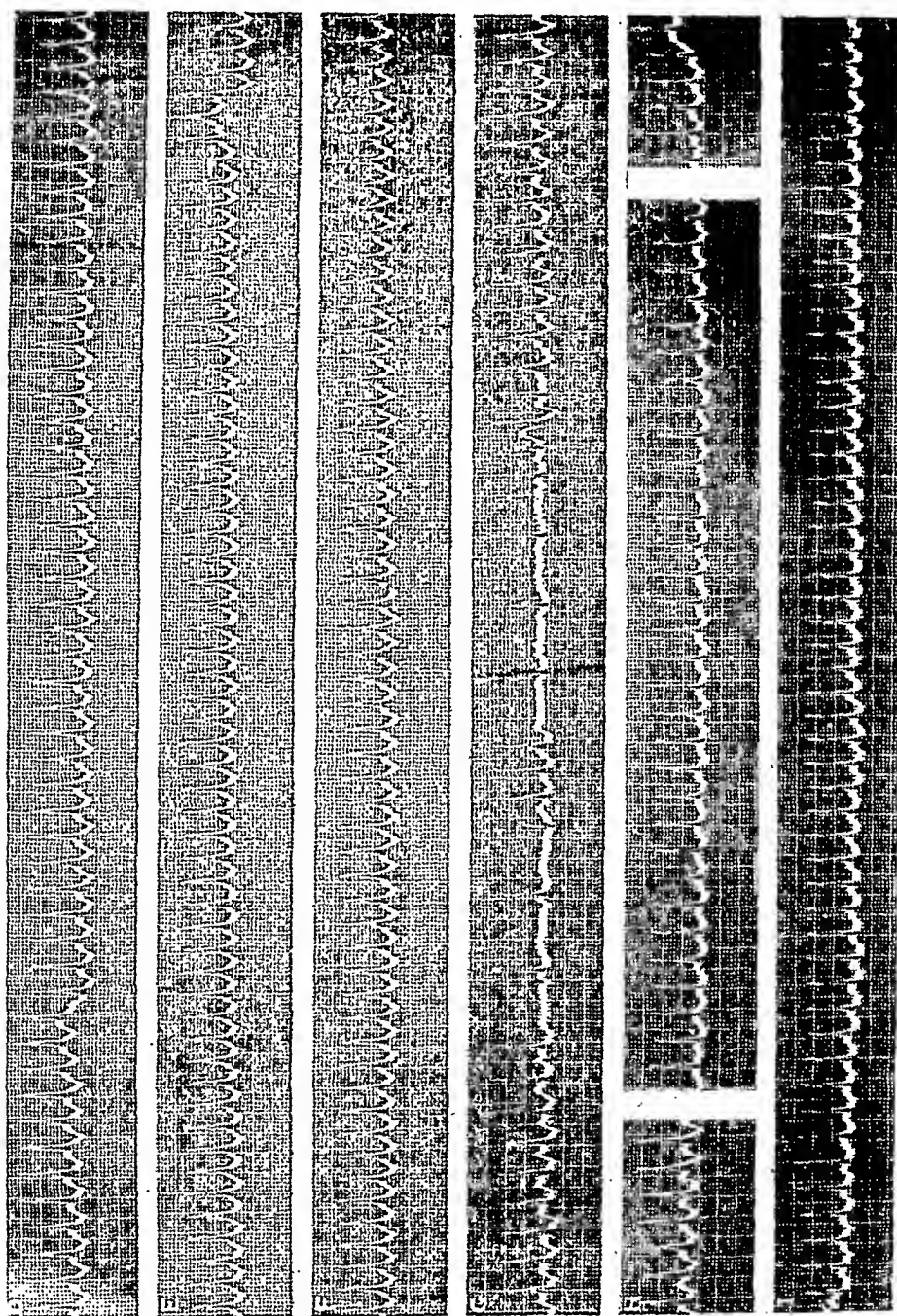


Fig. 2.

marked slowing of the rate. On discontinuation of the eyeball pressure the nodal tachycardia recurred (*B*). Eyeball pressure again was applied (*C*) and caused a return to regular sinus rhythm, with extrasystoles. When the eyeball pressure was released, a tachycardia ensued which was considered ventricular in origin because of the widening of the QRS complexes. The ventricular tachycardia continued for forty-five seconds, until section *G*, at which time eyeball pressure was again applied; this was followed by a return of regular sinus rhythm, with extra-

systoles (*G*, middle section). When the pressure was released, the ventricular tachycardia returned. The machine was stopped for a few minutes (break in *H*). When recording was resumed, the original nodal tachycardia was present (*H*, *I*, *J*). Records *K*, through *R*, revealed a similar abnormality. Eyeball and carotid pressure (*J*, *K*, *N*, *O*) resulted in a return to regular sinus rhythm, with extrasystoles, and, when the pressure was released, nodal or ventricular tachycardia would follow. The machine was stopped for a few minutes. When recording was resumed,

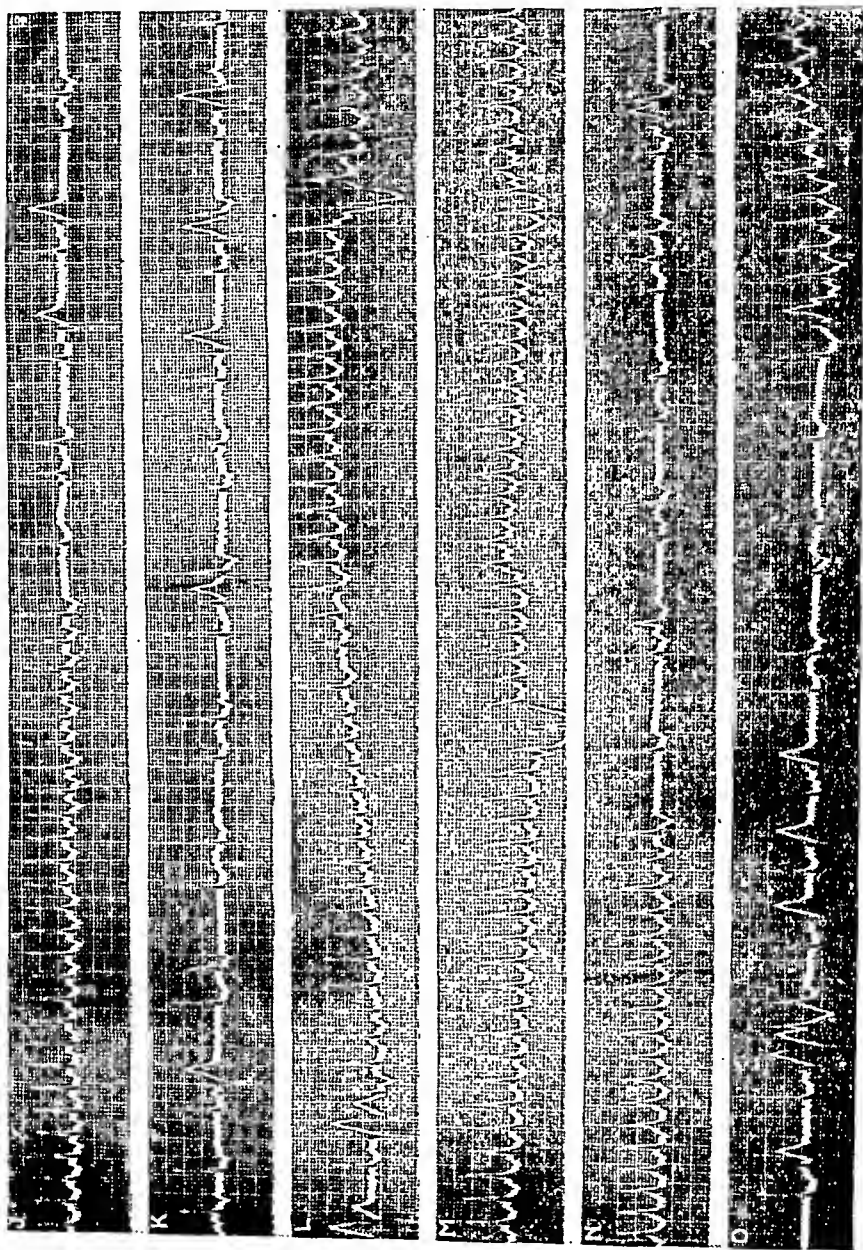


Fig. 3.

sustained eyeball pressure was applied at *R* (middle section), and regular sinus rhythm returned and persisted (*S*, *T*). Despite the regular sinus rhythm there were abnormalities of the T waves which were probably due to ischemia induced by the tachycardia.

Clinically, the patient was in a state of prostration throughout. She was markedly eyaunotic and dyspneic and had a thready pulse. The blood pressure was 60/40. After the return of the regular sinus rhythm, the cyanosis and

dyspnea disappeared and the patient was comfortable. The blood pressure at this time was 130/70. The next day an electrocardiogram showed regular sinus rhythm. On the tenth day post partum, the patient was fluoroscoped and a normal configuration of the heart was found. The basal metabolic rate was plus 8. No murmurs were audible. She was discharged in good health on the twelfth day post partum.

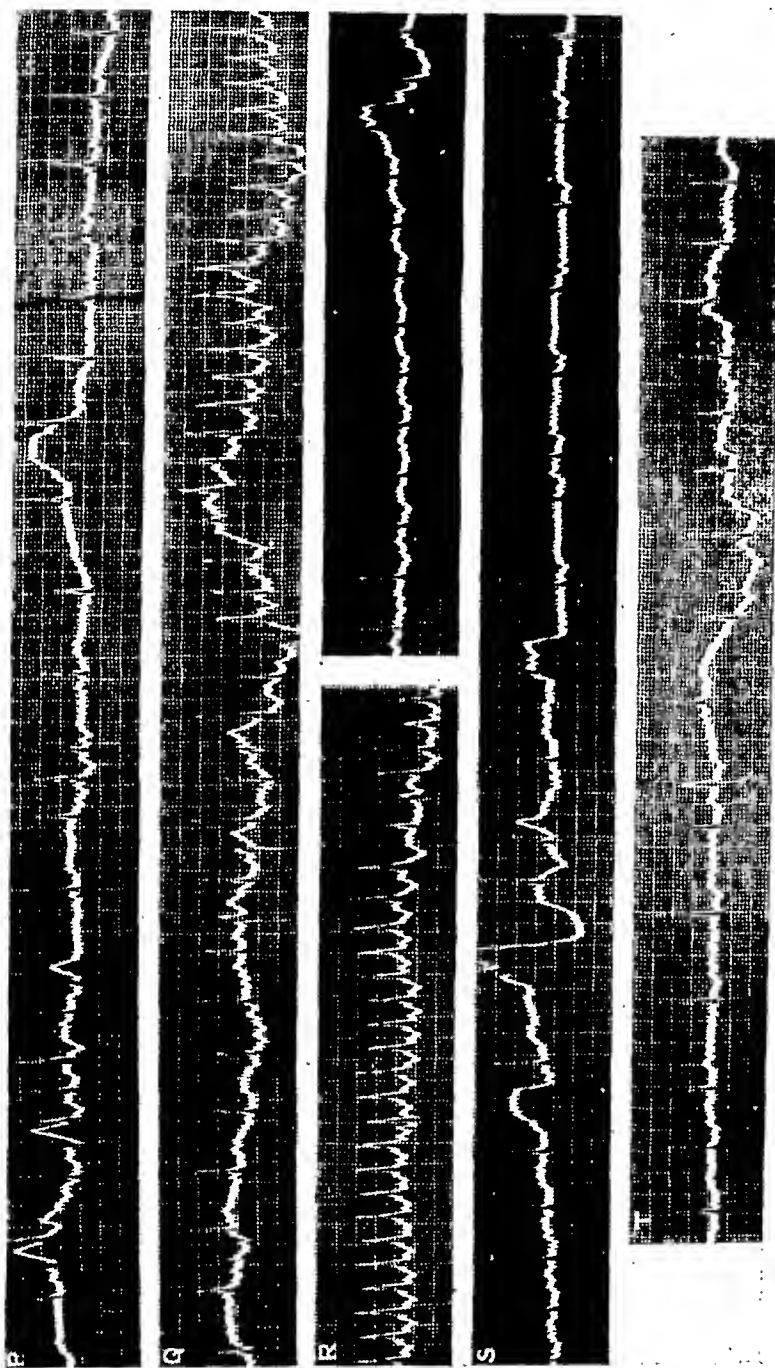


Fig. 4.

#### COMMENT

Collapse after delivery may be due to a variety of causes. It is very important to ascertain the exact etiology of the collapse in order that proper therapy may be instituted. In this particular case an abnormal tachycardia was suspected, and we were fortunate in obtaining com-



plete graphic studies which illustrate the course of events and the success of simple therapy. Despite the fact that the physical examination was negative, the patient probably had rheumatic heart disease. Although it is possible that a severe strain alone might cause such a tachycardia, it is more likely, in view of the history, that the rheumatic heart disease itself was a contributing factor.

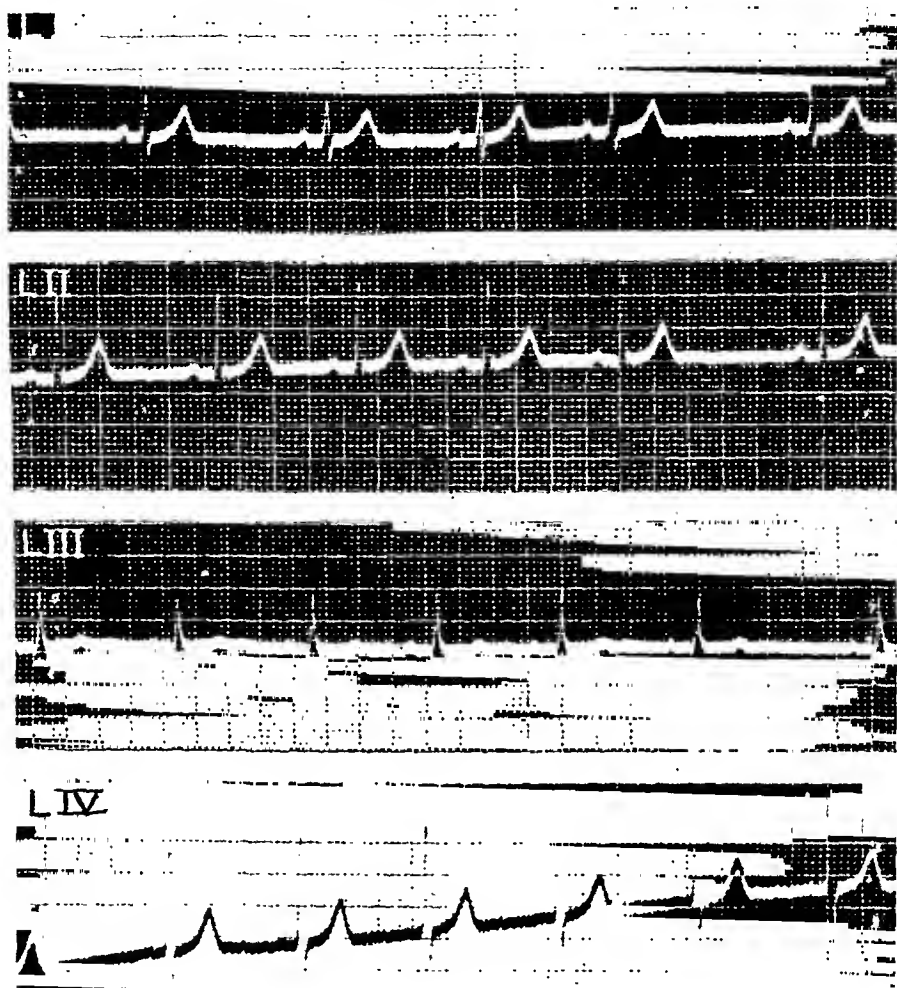


Fig. 5.

It is important to note that, in view of the electrocardiographic evidence, the collapse in this case was due to a central cardiac disturbance, rather than to the usual peripheral circulatory failure.

#### CONCLUSION

1. An interesting instance of tachycardia from varying foci which occurred after delivery is presented.
2. The value of electrocardiographic studies, during or after labor, in cases in which heart disease is suspected, is emphasized.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Ludden, J. B., Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: Effect of Testosterone Propionate and Estradiol Dipropionate on Experimental Atherosclerosis in Rabbits. *Arch. Path.* 33: 58, 1942.

In female rabbits fed cholesterol the development of hypercholesteremia was inhibited and the deposition of cholesterol in the aorta was prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol these steroids exerted little or no such protective action.

AUTHORS.

Kerr, W. J.: The Clinical Use of the Symballophone—an Improved Double Stethoscope for the Lateralization and Comparison of Sounds. *West. J. Surg.* 49: 632, 1941.

Some brief comments are made on the construction of the symballophone, a new stethoscope for the comparison and lateralization of sound. A few of the more important clinical uses of the symballophone are discussed.

AUTHOR.

Best, C. H.: Heparin and Thrombosis. *Bull. New York Acad. Med.* 17: 796, 1941  
Harvey Lecture, New York Academy of Medicine.

The author discusses the physical and clinical properties of heparin and its role in the prevention of thrombosis. He describes the value of heparin in the treatment of vascular accidents and injuries and in certain aspects of military surgery, a matter of considerable interest and importance at present.

McCULLOCH.

White, P. D., Chamberlain, F. L., and Graybiel, A.: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart. *Brit. Heart J.* 3: 233, 1941.

Inversion of the T waves in Lead II of the electrocardiogram, although most commonly the result of heart disease or toxic states, may be a normal physiologic variation in occasional persons, particularly those of asthenic habitus with vertical hearts and prone to neurocirculatory asthenia.

The position of the heart is the most important factor in producing this T-wave inversion which is found in the sitting or standing position but is corrected by recumbency or by elevating the diaphragm as at full expiration. Autonomic nervous influences comprise another factor, although less striking as a rule, the low or inverted T waves then being attended by tachycardia; any cause of such stimulation,

i.e., excitement, can then be responsible. Fear and anxiety may act through the production of overventilation with resultant alkalosis. Both heart position and nervous influences may be active in the same case.

The relatively common occurrence normally of inversion of the T waves in Lead II makes it imperative to recognize its existence in order to avoid erroneous diagnoses of heart disease.

AUTHORS.

Levinson, S. A.: *Congenital Heart Disease as a Cause of Sudden Unexpected Death in Children Under One Year of Age.* *Am. J. Clin. Path.* 11: 741, 1941.

In a series of 12,837 autopsies performed at the Cook County Hospital seventy-eight cases, or 0.607 per cent, and in 1,921 autopsies performed at the Research and Educational Hospital twenty-three, or 0.11 per cent, showed evidence of congenital heart disease. All of the children were under 1 year of age.

In a series of 8,500 cases investigated for the coroner's office of Cook County, there were eight which showed gross evidence of congenital heart disease, and these children under 1 year of age died suddenly and were never previously ill, or under a physician's care.

In the text is a discussion of the probable etiological factors, including meteorological alterations, which may play a role in congenital malformations of the heart.

AUTHOR.

Bettinger, H. F.: *Patency of the Ductus Arteriosus in Adults.* *M. J. Australia* 11: 418, 1941.

A new surgical procedure, admirably planned and performed at first by Gross, has given the opportunity to study the circulation in cases of patent ductus arteriosus by methods hitherto not applicable.

The conclusions drawn by Eppinger and Burwell from such studies are contradicted in part by findings in a case in which death resulted from a patent ductus arteriosus and by a number of statements in the literature. An explanation for these contradictions is offered on the basis of another mechanism of circulation, and the indications for surgical treatment of a patent ductus arteriosus are reviewed in the light of this explanation.

AUTHOR.

Bourne, G.: *Changes in Renal Function and Persistence of the Murmur After Ligature of a Patent Ductus Arteriosus.* *Brit. Heart J.* 3: 228, 1941.

A case of patent ductus arteriosus is described in which ligature of the ductus caused a marked increase in the diastolic pressure, associated with great impairment of renal function, and did not result in disappearance of the classical murmur.

The hitherto undescribed changes in renal function and the persistence of the murmur, after ligature, are reported so that in future cases these points may be further investigated. Careful renal function studies should be done before as well as after operation in such cases.

AUTHOR.

White, P. D.: *Enlargement of the Heart.* *New England J. Med.* 225: 571, 1941.

Cardiac enlargement should be suspected in patients whose hearts are under strain, even though they are free of symptoms; it is possible to do more good at



an early stage than after heart failure has set in. On the other hand, it is equally important not to establish cardiac neuroses thereby, and especially not to mistake for cardiac enlargement a heart size that is on the borderline of normal unless undue heart strain is or has been present.

AUTHOR.

Levine, S. A., and Rosenbaum, F. F.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. II. Ultimate Prognosis. *Arch. Int. Med.* 68: 1215, 1941.

A study was made of 372 patients who had recovered from an initial attack of acute myocardial infarction, in order to determine the type of progress that might be expected and to see whether any predictions as to prognosis could be made from the various clinical and electrocardiographic features.

Although the course that follows an acute myocardial infarction varies a great deal, there are some clinical features analyzed in this study which may aid materially in judging the prognosis.

AUTHORS.

Lyon, D. M.: The Significance of Systolic Murmurs. *Edinburgh M. J.* 68: 589, 1941.

A very large proportion of systolic murmurs are functional and innocent, but all demand the most careful study before they can be regarded as harmless. Many closely resemble organic murmurs and can be distinguished only with difficulty. In the study of a murmur its time, site, and propagation are most important, but the effects of respiration, posture, and cardiac rate should be specially noted. Several examinations may be required before a diagnosis is made, and no final decision should be taken until the pulse rate is within normal limits.

AUTHOR.

Blalock, A., and Burwell, C. S.: Chronic Pericardial Disease; Report of Twenty-Eight Cases of Constrictive Pericarditis. *Surg. Gynec. & Obst.* 73: 433, 1941.

Twenty-eight examples of constrictive pericarditis are reported. The alterations of the circulation resulting from this condition are described. The etiology, diagnosis, course, and treatment of the twenty-eight patients are made the basis of a consideration of these aspects of this variety of pericardial disease. For the sake of completeness there is added a brief discussion of mediastinopericarditis.

AUTHORS.

Killian, S. T., and Calvin, J. K.: Renal Hypertension in Children: Clinico-pathologic Studies. *Am. J. Dis. Child.* 62: 1242, 1941.

The case histories of children with persistent arterial hypertension admitted to the Sarah Morris Hospital for Children of Michael Reese Hospital during the past eleven years have been studied. Only those in which one or both kidneys were available for pathologic investigation have been selected for detailed analyses, and only one of the three cases of hypertension due to subacute or chronic glomerulonephritis has been included. Although chronic glomerulonephritis is usually accompanied by hypertension, it is a relatively less frequent cause of hypertension in children than was heretofore assumed.

Six cases of renal hypertension are reported in detail, with clinical and pathologic observations. In four the kidneys were obtained for study at autopsy, and in two

a kidney was removed at operation. The diagnoses in the cases were as follows: (a) congenital unilateral hypoplasia of the kidney with nephrosclerosis, (b) chronic bilateral pyelonephritis with contraction of the kidneys, (c) chronic bilateral pyelonephritis with arteriolonecrosis, (d) bilateral hydronephrosis with chronic pyelonephritis, (e) traumatic rupture of hydronephrotic kidney, and (f) subacute glomerulonephritis with arteriolonecrosis.

An attempt is made to explain the hypertension on the basis of the pathologic observations in the light of the newer concepts about the physiologic aspects of hypertension. The interference with the renal vascular supply which was shown anatomically could have been responsible for the hypertension in each case.

In the majority of these cases the disease might have responded to urologic management if the hypertension had been detected in its early stages before irreversible damage had occurred, or if the renal condition had been diagnosed even before the hypertension became manifest.

In the majority of the cases of persistent hypertension in children in which the kidneys have been examined pathologically the disease was of renal origin.

AUTHORS.

Klinefelter, H. F.: The Heart in Sickle Cell Anemia. *Am. J. M. Sc.* 203: 34, 1942.

No cause other than the profound anemia is found to explain the cardiac changes in patients with sickle cell anemia. The mechanism by which any anemia produces changes in the heart is not entirely understood, but it seems probable that the hypertrophy and dilatation are compensatory for the prolonged anoxemia.

The cardiac changes of patients with sickle cell anemia are more marked than the changes found in other anemias. This is because sickle cell anemia is somewhat unique in the long duration of such a severe degree of anemia.

The prolonged A-V conduction time is probably due to increased vagal tone, which also appears to be secondary to, or compensatory for, the prolonged anoxemia.

Although the clinical picture may closely resemble rheumatic fever, there is no proved instance of the two diseases occurring together. From the available data, there is no need to regard these patients as uncommonly liable to rheumatic fever.

AUTHOR.

Lisa, J. R., Solomon, C., and Eckstein, D.: The Heart in Combined Syphilitic Aortic Valvulitis and Rheumatic Heart Disease. *Arch. Path.* 33: 37, 1942.

Fourteen cases of combined syphilitic aortic valvulitis and rheumatic heart disease are reported. In nine instances the aortic valve was affected by both a syphilitic and a rheumatic process. Ten of the hearts had some degree of involvement of the coronary ostia by syphilis. The myocardium was affected by a multiplicity of lesions. The course tended to be of short duration and was usually intractable to therapy. A clinical diagnosis of the combined disease is difficult to make. It should be suspected in the patient with cardiac disease when a history of both rheumatic fever and syphilis is obtained in a patient known to be rheumatic with a course more intractable than usual if there is a positive serologic or clinical evidence of syphilis and in a patient with recognized syphilis when the physical findings are those of rheumatic heart disease. The roentgenologic examination can be of great value.

AUTHORS.

Frolkis, N. K.: Cardiac Disease and Foci of Infection. Ohio State M. J. 37: 1045, 1941.

Twenty-nine cases of rheumatic heart disease were observed during the course of physical examination of 270 apparently normal persons. Because these persons were all quite young no cardiac embarrassment was noted. None of the persons who were examined knew before being examined that he had cardiac disease.

Examination of the common foci of infection showed nothing of significance when comparison studies between the cardiac group and the normal control group were made. Although this study is far from complete, it makes one wonder whether or not the theory of foci of infection in rheumatic heart disease has been ascribed its rightful importance.

The importance of the routine physical examination is well pointed out by the above findings.

AUTHOR.

Boharas, S., Hollander, L., and Goldsmith, M.: The Early Diagnosis of Syphilitic Aortitis. Am. J. M. Sc. 203: 54, 1942.

The authors have attempted to repeat previously emphasized methods of examination to determine their value in the diagnosis of early or uncomplicated syphilitic aortitis. Two hundred patients with syphilis and 200 patients as normal controls were used for this purpose. The authors' conclusions are as follows:

There is no single pathognomonic sign of early syphilitic aortitis discernible either by roentgen ray, electrocardiogram, or physical examination.

It is impossible at present to make a positive clinical diagnosis of early syphilitic aortitis.

Roentgen ray examination is a valuable aid in the diagnosis of late aortitis, at times being the first or only indication that such a condition exists.

AUTHORS.

Kimmel, G. C.: Hypertension and Pyelonephritis of Children. Am. J. Dis. Child. 63: 60, 1942.

Hypertension associated with chronic pyelonephritis in children is not rare; it was present in about 10 per cent of seventy-five cases.

Nephrectomy or the relief of obstruction to urinary flow in cases of unilateral pyelonephritis and hypertension frequently is followed by a fall in blood pressure to a normal level.

There is no correlation between the level of urea in the blood and the blood pressure.

Many pyelonephritic kidneys show slight to moderate degrees of arteriolosclerosis in the presence of normal blood pressure.

AUTHOR.

Laufer, S. T.: Orthostatic Hypotension. Canad. M. A. J. 46: 160, 1942.

A case of orthostatic hypotension with definite neurological signs involving the central nervous system from an influenzal type of encephalitis is reported. The effects of atropine, pilocarpine, epinephrine, ephedrine, and benzedrine are described. The vertigo was favorably influenced by small amounts of benzedrine combined with the "head-up" treatment of MacLean and Allen.

A brief discussion of orthostatic hypotension and a suggested classification of the different varieties from an etiological viewpoint is given.

AUTHOR.

Watkins, A. G.: Congenital Arteriovenous Anastomosis. Brit. M. J. 11: 849, 1941.

The unusual and puzzling feature of this case was the milky discharge, and no reference to a similar happening has been found in the literature. Unfortunately this cleared up so quickly that we were unable to make full observations on it, but its presence pointed to an increased flow of lymph in the limb. The close embryonic relation between lymphatic vessels and veins, which are both derived from a common capillary plexus, may have produced a lymphatic developmental disturbance with increase in the lymph channels, or the greater lymph flow may simply have been the result of an increased blood supply to the limb. No edema of the limb was present when the patient was first seen, and we do not know whether there had been any before the discharge.

The most striking clinical feature of these cases is the increased growth of the limb, affecting bones and soft parts. Paterson and Wyllie (1925) suggested that this is due to an increased vascularity at the growing ends of the tibia and femur. Experimental section of the sympathetic nerves of limbs of kittens, as described by Harris and Wright (1930), although producing a greater blood supply, did not increase their growth. When the cervical sympathetic nerve and ganglia were removed in a rabbit's ear, some increase in growth was noted after 100 days, and those authors suggested that it may be the higher temperature of the limb that acts as a stimulus.

The exact cause of the hypertrophy is still far from clear, and the presence of the lymphatic discharge in the above case must remain unexplained until a recurrence of the discharge allows later investigation, or further cases have been observed.

AUTHOR.

Pedley, F. G.: Coronary Disease and Occupation. Canad. M. A. J. 46: 47, 1942.

The author gives a tabular record of mortality from diseases of the coronary arteries and angina pectoris in Canada since 1931. The table shows an increase from 1,937 males and 923 females in 1931 to 4,978 males and 2,271 females in 1938. These figures represent an understatement rather than an overstatement of the actual picture. Vital statistics alone do not settle the question whether coronary disease is on the increase or not. Figures are not available which would enable one to calculate the occupational incidence of coronary disease. The author reviews the available data on the subject and presents a tabular analysis of fifteen specific occupational groups. The lowest group of agricultural and garden workers shows less than one-ninth of the rate among the highest group of physicians and surgeons.

McCULLOCH.

Keys, A., and Violante, A.: The Cardio-Circulatory Effects in Man of Synephrin Tartrate (*dl*- $\alpha$ -hydroxy- $\beta$ -methylamino-4-hydroxy-ethylbenzene hydrochloride). J. Clin. Investigation 21: 13, 1942.

A study has been made, under controlled environmental and physiologic conditions, of the cardiocirculatory effects in man of racemic synephrin tartrate.

The threshold subcutaneous dosage is about 100 mg., and the indicated therapeutic dosage for pressor action is about 400 mg. given subcutaneously.

In normal man synephrin tartrate produces a marked rise in systolic blood pressure, a slight rise in diastolic blood pressure, and a slight fall in pulse rate. With subcutaneous administration these effects are at a maximum in ten to thirty minutes after injection and persist in diminishing degree for more than an hour.

Synephrin tartrate produces a well-marked rise in stroke output of the heart and an increase in the minute volume. The arm-to-tongue circulation is shortened.

The systolic heart size is slightly diminished with therapeutic doses of synephrin tartrate. The electrocardiogram is generally unaltered, but occasionally the P wave may be depressed. No irregularities in heart action have been seen in any of our studies.

It is believed that synephrin tartrate is intermediate between epinephrine and neosynephrin in its relative sympathetico-parasympatheticomimetic action.

AUTHORS.

Hueper, W. C.: *Experimental Studies in Cardiovascular Pathology. IV. Methyl Cellulose Atheromatosis and Thesaurosis.* Arch. Path. 33: 1, 1942.

The intravenous injection of a solution of methyl cellulose into dogs causes hematologic reactions which may be designated as the hematologic macromolecular syndrome (reduction in number of erythrocytes, in amount of hemoglobin, in volume of packed erythrocytes; acceleration of coagulation and sedimentation of erythrocytes; lengthened coagulation time; acute transitory leucopenia; persistent myeloid leucocytosis; increased viscosity of plasma).

The chemical inertness of the injected substance and the inability of the body to degrade the macromolecular compound and thereby to facilitate the elimination of the substance lead to retention and accumulation of methyl cellulose in the liver, spleen, lymph nodes, kidney, and vascular wall (thesaurosis).

The arteries of rabbits and dogs given injections of a solution of methyl cellulose over long periods show extensive atheromatous changes of an apparently methyl cellulose nature. Medial degeneration and calcification appear underneath these intimal lesions.

Methyl cellulose atheromatosis is the result of an impairment of the oxygenation and nutrition of the vascular wall caused by the formation of methyl cellulose films on the surface of the intima and of the erythrocytes. This causative mechanism is common to the dynamics of atheromatosis in general.

AUTHOR.

Taquini, A. C.: *Comparative Studies on the Action of Ephetonin in Normal and Hypertensive Subjects.* Revista Argent. de Cardiol. 8: 241, 1941.

As ephetonin potentiates the pressor effect of hypertensin in the dog, it was thought that its injection into hypertensive patients would produce a greater pressor effect than in normal persons, if hypertensin were present in their circulation.

Intravenous injection of ephetonin (0.025 Gm.) in ten normal and fifteen hypertensive subjects produced a rapid rise in arterial pressure without any untoward manifestations. Ten of the hypertensive patients had a more or less constant level of blood pressure. In these the rise in pressure was the same as in the ten normal subjects (average 21.9 and 20.1 mm. Hg, respectively). In the five patients of the hypertensive group which showed wide spontaneous oscillations in the level of resting blood pressure, the rise elicited by ephetonin was much greater (average 39 mm. Hg).

The blood pressure rise was of shorter duration in the hypertensive group.

Consideration of the regulating mechanism involved led to the conclusion that these results afford no conclusive evidence for or against the existence of hypertensin in the blood of hypertensive patients.

AUTHORS.

## Book Review

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CARDIAC CLINICS. A Mayo Clinic Monograph: By Fredrick A. Willius, B.S., M.D., M.S., in Med., Head of Section of Cardiology, Mayo Clinic, and Professor of Medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. The C. V. Mosby Company, St. Louis, 1941, 276 pages, 35 illustrations, \$4.00.

This is an excellent book. It fulfills in admirable fashion the author's guiding desire "to present concise practical discussions dealing with the heart, intended primarily for the busy practitioner of medicine." The case records are those of patients at the Mayo Clinic; the discussions are those of an alert clinician of vast experience whose philosophy has been moulded by a sympathetic understanding of the manifold needs of the patient with heart disease.

The book is attractively bound and is printed on good paper. It is not too large, and the various sections are not too long, since it is not a textbook. In order to achieve its purpose such a volume must be concise. There are in it many of the kernels that might be gleaned from a more comprehensive text only at the expense of considerable time.

Such a book necessarily must avoid lengthy discussion in a particular case, even at the risk of being somewhat didactic or of omitting statements of general principles which upon occasion might helpfully be applied to somewhat different cases of the same class. To a remarkable degree such faults are avoided. In a brief discussion of congestive heart failure the author says that "unless some contraindication exists, administration of digitalis is instituted," a principle regularly followed in the cases of failure described. In the discussion of a particular instance of congestive failure, however, in which auricular fibrillation also was present (page 51), the indication for digitalis might appear to be referred more to the presence of the fibrillation with ventricular tachycardia and large pulse deficit than to the congestive failure itself. Whatever minor reservations in theory the reader might entertain, there can be little room for disagreement regarding the general application of therapeutic procedures in the various cases under discussion. No better models of treatment could be followed in practice.

The cases and discussions are grouped so as to embody chapters on the various types of heart disease, making fourteen chapters in all. But the book is not merely a compilation of specimen cases vividly described and managed with consummate skill. It is much more than that. There are such sections as "Cardiac Murmurs," "Recognition of the Normal Heart," "The Healing of Cardiac Infarcts," "The Regulation of Diet in Heart Disease," and "The Philosophy of Convalescence."

The last section is entitled "The Science and Art of Medical Practice." Not only in it, however, but all through the book the author is revealed as one "whose experience has endowed him not only with the science, but amply with the art of medicine." Everyone who treats patients with heart disease would do well to read this book.

DREW LUTEN.

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A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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## Original Communications

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### THE GRAPHIC REGISTRATION OF THE NORMAL HEART SOUNDS

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#### A GRAPHIC ANALYSIS OF THE NORMAL HEART SOUNDS

**I**N A previous paper,<sup>1</sup> we discussed the acoustic principles involved in auscultation and the mechanisms that are effective in acoustic stethoscopes, electrical stethoscopes, and phonocardiographs. The discussion which follows is a continuation of this paper, and is intended to clarify the problems involved in auscultation and phonocardiography, with greater emphasis upon the clinical aspects.

Many relationships and phenomena exist in auscultation and phonocardiography which are not well understood. For example, it is evident from a review of the literature of the graphic registration of heart sounds that there are inconsistencies in the reported observations, relating chiefly to (1) The maximum and minimum duration of the normal heart sounds, (2) the intervals between certain of the normal heart sounds, (3) the intensity relationships of normal heart sounds, (4) the number of vibratory oscillations that compose the normal heart sounds, and (5) the frequency and pitch of the major components of normal heart sounds. It is the purpose of this study, therefore, to ascertain and analyze the causes for such divergences in phonocardiographic measurements and to attempt to arrive at more accurate evaluations.

We believe that these evaluations are necessary in order to explain the characteristics of auscultatory and phonocardiographic instruments and to place suitable limitations upon any single method of investigation.

#### ACOUSTIC CONSIDERATIONS

When a patient is ausculted with the usual stethoscope, the observer definitely does not hear the cardiac sound vibrations as they actually exist at the source because of three major forms of distortion, namely:

1. The heart sounds are modified in their path of travel from the source to the surface of the chest.

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2. The vibrations that reach the surface of the chest are further modified by the stethoscope and type of chest piece employed.

3. The human hearing mechanism (that is, the ear, the nervous pathways, and the brain) additionally modifies the heart sound vibrations.

The study of acoustics as related to auscultation, therefore, deals with the vibrations or disturbances set up in the chest and their transmission through the structures of the chest, as well as through the stethoscope, and with the resulting auditory perceptions.

*Characteristics of the Chest in Sound Transmission.*—Sound, which is the result of vibration of a medium, is capable of traveling through a solid, liquid, or a gas as a compressional wave, unless the medium is entirely inelastic. In other words, the ability of sound to travel through matter depends upon the elasticity, viscosity, and density of the medium. If the effects of viscosity are small, as is the case with water, air, metal, and bone, the sound energy may be transmitted with little loss. In some media, such as soft rubber or fatty breast tissue, the sound waves are almost immediately suppressed.

In a homogeneous substance, a sound wave will propagate itself at a velocity the magnitude of which depends upon the physical properties of the medium. The attenuation of the wave is governed by the viscosity and the spreading of the sound energy as the wave progresses. When sound energy travels from one medium into another of different physical properties, or when there is no longer homogeneity of the medium, transmissional losses in the form of refraction and reflection take place. Some media are capable of transmitting low frequency vibrations with less attenuation than high frequencies, and vice versa; this results in distortion of the sound.

There are many paths along which heart and chest sounds travel in the human body before they reach the surface. A considerable percentage of the sound energy never reaches the surface because of viscosity, elasticity, density, spreading, reflection, and refraction losses. Naturally, the intensity of the sound is maximum over the portion of the chest where the sound follows a path of minimum attenuation, and this location the physician normally selects with his stethoscope. Auscultatory experience has shown that murmurs produced by lesions of the four valves of the heart are heard with maximum intensity in certain areas of the chest, although there may be other sections of the chest surface which are closer to the valves under consideration.

The degree of modification to which heart sound vibrations are subjected as a result of transmissional losses is dependent upon the physical structure of the patient's chest. Transmissional losses in the average adult differ from those in a thin-chested child, an emaciated person, or an obese or barrel-chested subject.

*Stethoscope Characteristics.*—The stethoscope is a device which forms a closed acoustic system for conducting sounds by air transmission from the surface of the chest to the observer's ear. The experimental data obtained by Johnston and Kline<sup>2</sup> indicate that sound vibrations are altered by the acoustic stethoscope; we<sup>1</sup> have also demonstrated that every type of acoustic stethoscope modifies the sound vibrations in their passage from the chest wall to the ear.

The degree to which the heart sound vibrations are modified by the stethoscope depends to a considerable extent upon the type of chest piece employed. Our conclusions<sup>1</sup> on stethoscopic chest piece characteristics are:

“1. The open stethoscopic chest piece, or bell, when applied to the patient's chest, may be considered as a diaphragm type of chest piece. The skin which is bounded by the lip of the bell forms the diaphragm, and the fleshy portion under the skin acts as a damping medium.

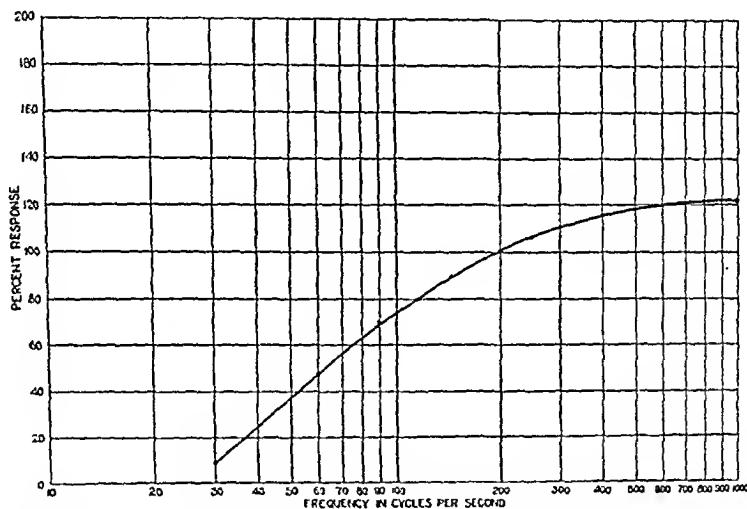


Fig. 1.—Frequency response characteristic of the average of a large number of acoustic stethoscopes, minus the effects of the chest piece. (After Rappaport and Sprague.<sup>1</sup>)

“2. The larger the diameter of the open stethoscopic chest piece, the better its response to low-pitched sounds. This is accomplished at the expense of the higher frequency components.

“3. The greater the pressure with which the open stethoscopic chest piece is applied to the patient's chest, the better is the response of the stethoscope to higher frequency components. Thus, by varying the application pressure, the physician exerts a variable selective action upon the sounds because the natural period of the skin diaphragm which is bounded by the chest piece depends on the pressure with which it is applied.

“4. The principle of operation of the Bowles (diaphragm) chest piece is similar to that of the open bell, except that additional attenuation of

the lower pitched heart and chest sound components is accomplished by the action of the rigid diaphragm of the Bowles chest piece."

Fig. 1 shows the manner in which the average of a large number of stethoscopes modifies the heart sound vibrations with respect to frequency. This curve does not include the modifying effects of the stethoscopic chest pieces. The frequency response characteristic of any single acoustic stethoscope is not as regular as in Fig. 1 because all acoustic stethoscopes possess resonance peaks which superimpose themselves upon the smooth average curve.

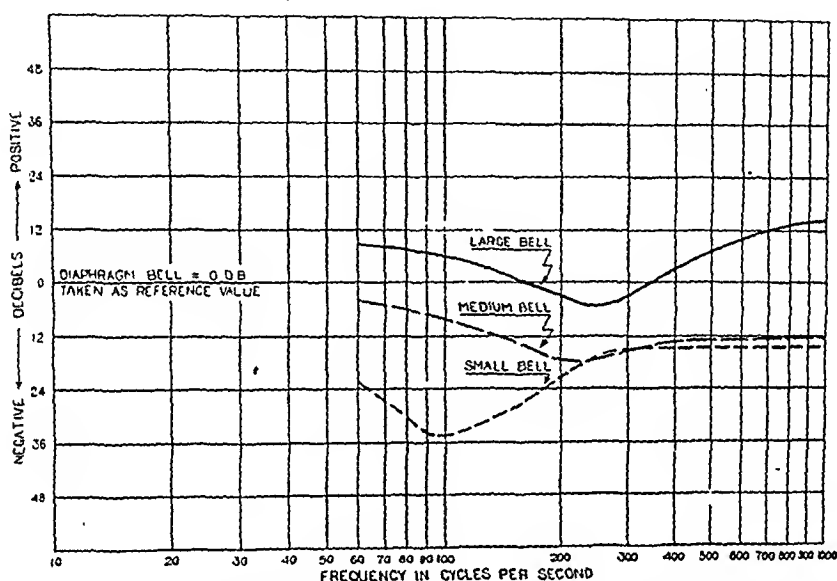


Fig. 2.—Resultant curves of the three open chest pieces of Fig. 3, as compared with diaphragm chest piece (Bowles). The higher the decibel reading, the higher the relative efficiency of the chest piece. (After Rappaport and Sprague.)



Fig. 3.—Photograph of three open and one "Bowles" diaphragm chest pieces represented in Fig. 2. The dimensions of the bells are as follows: The lip diameter of the large open bell is 2.0 inches; of the medium open bell, 1.5 inches; and of the small bell, 1.0 inch. The "Bowles" chest piece employs a diaphragm 0.015 inch thick and a freely working diameter of  $1\frac{3}{8}$  inches. The internal volume of the large bell is 12.7 c.c.; of the medium bell, 6.2 c.c.; of the small bell, 2.3 c.c.; and of the diaphragm bell, 2.5 c.c.

Fig. 2 shows the approximate relative efficiency of the four chest pieces of Fig. 3 with respect to frequency, as ascertained by us.<sup>1</sup> Some of the

more important conclusions that may be drawn from these curves are as follows:

"1. The efficiency of the three open bells improves, with respect to that of the diaphragm bell, as the frequency is decreased.

"2. The larger the diameter of the open bell, the more efficient is the bell at the lower frequencies.

"3. The large bell exhibits a resonance effect in the upper auscultatory region that is characteristic of a Helmholtz resonator of such dimensions. The resonance points of the smaller bells are above the auscultatory range and therefore are not shown in the graph."

*If a summation of the frequency response curves of the average acoustic stethoscope and any of the chest pieces is taken, the over-all frequency response curve may be ascertained. Obviously, as the resultant curve is not linear, the sounds must be altered before reaching the observer's ears.*

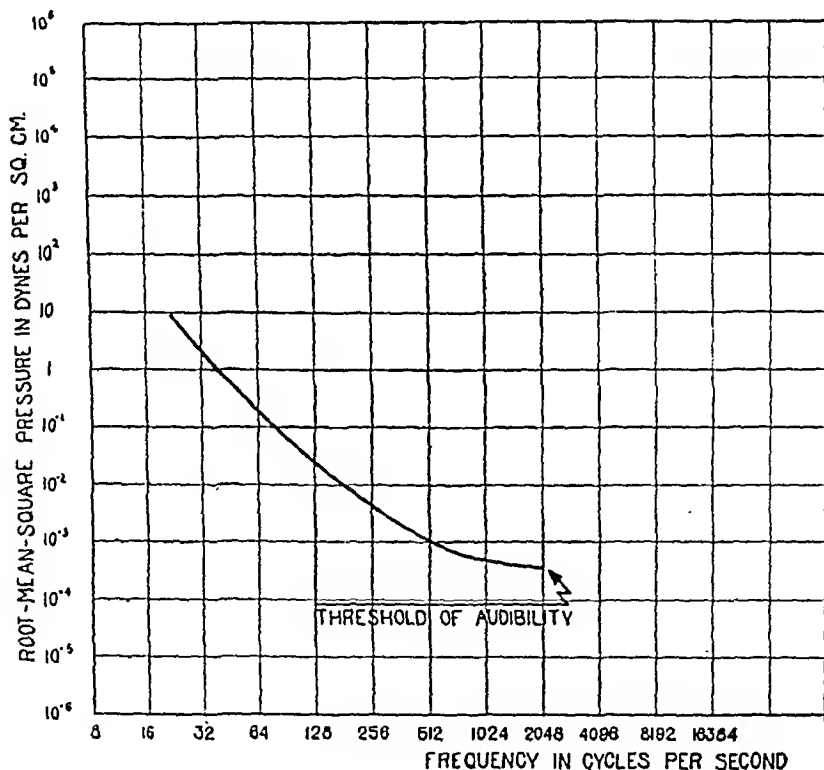


Fig. 4.—Average audiogram obtained from a large number of persons with normal hearing.

*The Human Hearing Mechanism.*—A characteristic of average normal hearing is the inability of the human ear to perceive as of equal loudness sounds of differing frequency which possess the same intensity. A graphic representation of this nonlinear characteristic of human hearing is known as an audiogram, and is obtainable by plotting as ordinates the minimum perceptible sounds applied to the tympanum of the ear

(expressed in dynes per square centimeter or bars), and as abscissae their frequency in cycles per second. Fig. 4 is an average audiogram (heart sound range) which was obtained on a large number of persons with normal hearing. The individual audiogram is not so smooth; peaks and valleys are superimposed. In addition, only rarely are two pairs of ears found to react alike, or even the two ears of any one person.

The curvature of the average normal audiogram approximates what is mathematically known as a logarithmic curve. *Thus, we may conclude that the human hearing mechanism alters or distorts logarithmically, with respect to frequency, the relative intensities of the components of the sounds that are transmitted to the tympanum of the ear by the stethoscope.*

The human hearing mechanism is capable of functioning over an enormous range of sound pressure or sound energy variations. For example, as shown in Fig. 4, at 20 cycles per second it takes about 10,000 times as much pressure to produce a "just perceptible" sound as it does at 512 cycles per second. A logarithmic representation of such enormous variations is shown in Fig. 4, and allows easier visualization.

#### PHONOCARDIOGRAPHY

Some knowledge of the presence of heart sounds and their value in cardiac diagnosis may date back to Hippocrates' work, *De Morbis*, in which vague reference to "immediate" auscultation is made. William Harvey, however, was one of the first to give convincing information about the presence of heart sounds (*De Motu Cordis*). It was not until 1819 that the character of heart sounds under normal and pathologic conditions was described by Laënnec,<sup>3</sup> who employed "mediate" auscultation in obtaining his data. Laënnec's observations were purely qualitative, as it was obviously impossible for him to make any positive measurements with his monaural stethoscope. His explanation of the mechanism of the heart sounds was incorrect because he attributed the first sound to ventricular contraction and the second to auricular contraction.

Hürthle,<sup>4</sup> in 1893, described a method of registering graphically the apex beat and the instant of occurrence of the first heart sound. The apparatus consisted of a microphone which excited an induction coil; this in turn excited a frog nerve-muscle preparation, which scratched a tracing on a smoked screen. In 1894, Einthoven and Geluk<sup>5</sup> substituted a capillary electrometer for Hürthle's frog nerve-muscle preparation and obtained the first graphic representation of the vibrations comprising the first heart sound. Some years later, Einthoven substituted the string galvanometer for the capillary electrometer, which decidedly increased the accuracy of the method.

Frank,<sup>6, 7</sup> in 1904, started a series of experiments with the object of devising a nonelectrical method for the graphic registration of the heart

sounds. He ultimately evolved what is known as the "Frank segment capsule," which has since proved useful in sphygmography as well as phonocardiography.

With the perfection of electronics, microphonic transducers, and galvanometric registering systems, improved electrical stethographs or phonocardiographs have come into use.

*Normal Phonocardiographic Characteristics.*—It is obviously impossible to control or standardize the transmissional properties of sound vibrations in chests of different persons. In phonocardiography, as well as stethoscopic auscultation, this variable must be tolerated. On the other hand, it is possible to control the operational characteristics of the phonocardiograph and stethoscope; they may be operated under standard conditions, provided suitable, universally accepted standards are selected. The characteristic of average normal hearing, as represented by the logarithmically shaped audiogram (Fig. 4), may also be considered as a constant. At the present time, there are no standard specifications for either the phonocardiograph or the stethoscope. This is certainly a deplorable situation when we consider that the stethoscope, especially, is one of the most widely used of medical instruments.

Throughout the literature, very little consideration has been given to the manner in which phonocardiographic measurements are related to the over-all frequency response of the phonocardiograph. In this study, three distinct types of phonocardiographic registration have been employed; namely, (1) linear, (2) stethoscopic, and (3) logarithmic. The resultant phonocardiograms have been compared.

The linear registration system possesses properties whereby sounds which are detected at the surface of the chest are not attenuated or accentuated with respect to frequency from practically zero cycles per second to above 1,000 cycles per second—the heart sound vibratory frequency band.<sup>1</sup> *Linear phonocardiography thus registers graphically the mechanical vibrations set up by cardiac action as they exist on the surface of the patient's chest—that is, the deviation of the recording galvanometer beam is proportional to the intensity of the vibration at the surface of the chest.* Obviously, in such a record, the large intensity, low frequency vibrations must be controlled by reducing the over-all sensitivity of the system, for their amplitude might be 10,000 times as great as that of the minimum recorded sounds. In such a system, therefore, high-pitched vibrations are often not recorded at all.

*The stethoscopic system of phonocardiographic registration<sup>1</sup> does not register the cardiac sound vibrations as they exist on the surface of the patient's chest, but as they are presented to the ears of an observer by an average acoustic stethoscope.\** The over-all frequency response of

<sup>1</sup>By stethoscopic effect is meant the attenuation effects introduced at different frequencies by the stethoscope tubing and binaural ear pieces, but in each record there is the added effect of the chest piece used in the registration.

the stethoscopic system (Fig. 1) is not linear, but possesses a rising characteristic with respect to frequency increase over the heart sound frequency band—that is, the higher the pitch of the sound, the better it is transmitted.

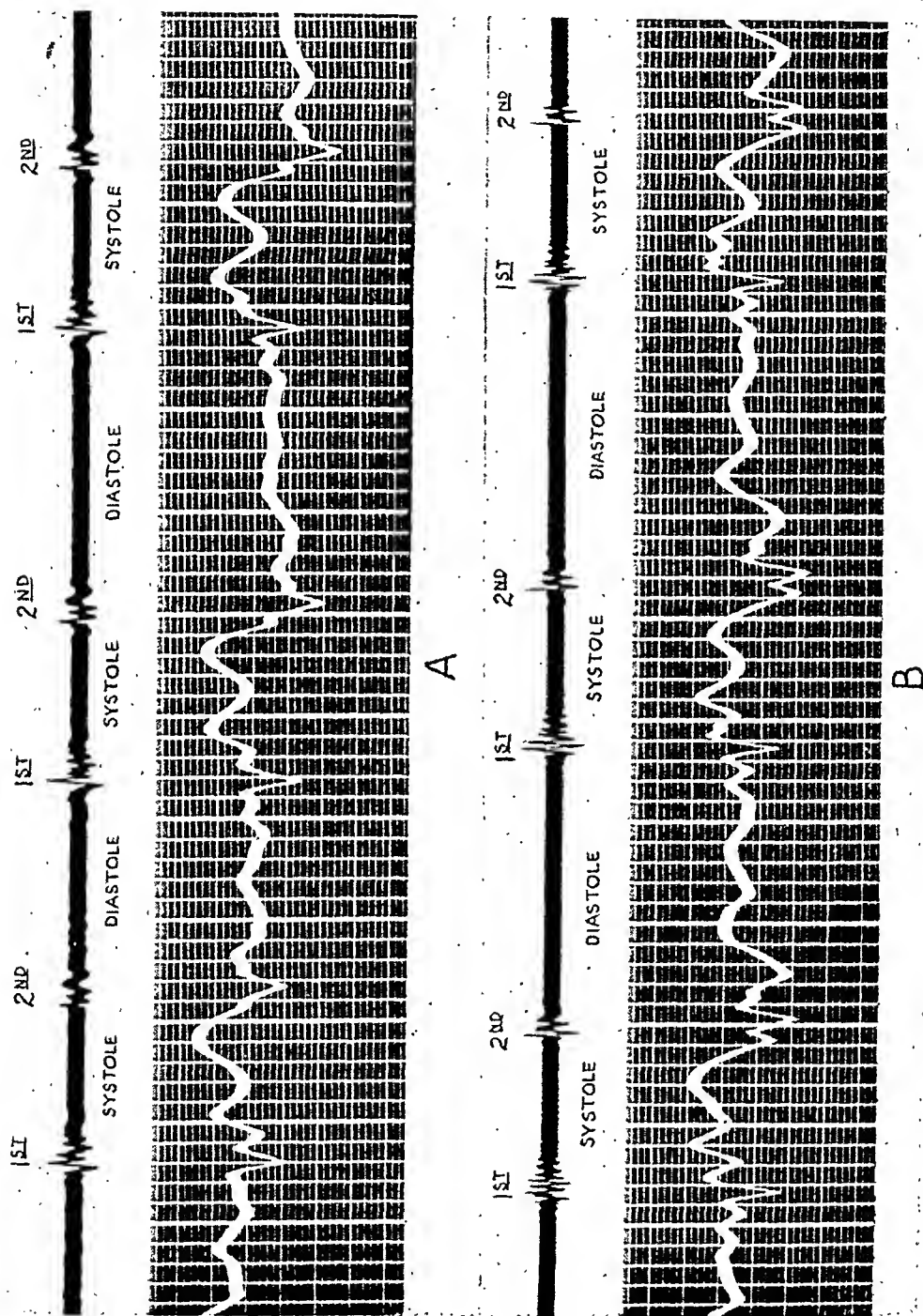


Fig. 5.—A, Simultaneous registration of stethoscopic (upper) and linear (lower) phonocardiograms on a normal person. B, Simultaneous registration of logarithmic (upper) and linear (lower) phonocardiograms on the same person as in A.

The logarithmic system<sup>8</sup> of phonocardiographic registration possesses an over-all frequency response equivalent to the summation of the curve of the average human audiogram (Fig. 4) and the curve of the average acoustic stethoscope (Fig. 1). The resultant logarithmic phonocardiogram is thus a graphic representation of the cardiac sound vibrations as

they are perceived by the average observer of normal hearing when an average acoustic stethoscope is employed.

The section on "Human hearing mechanism" will explain the use of the term "logarithmic" as employed here. The resulting graphic registration can be considered as a "human audiographic" record in which the amplitudes of the component sounds are registered in proportion to their relative loudness. That is, if the first heart sound, as heard, is twice as loud as the second heart sound, the amplitude of the graph of the first heart sound will be twice as great as that of the second heart sound.

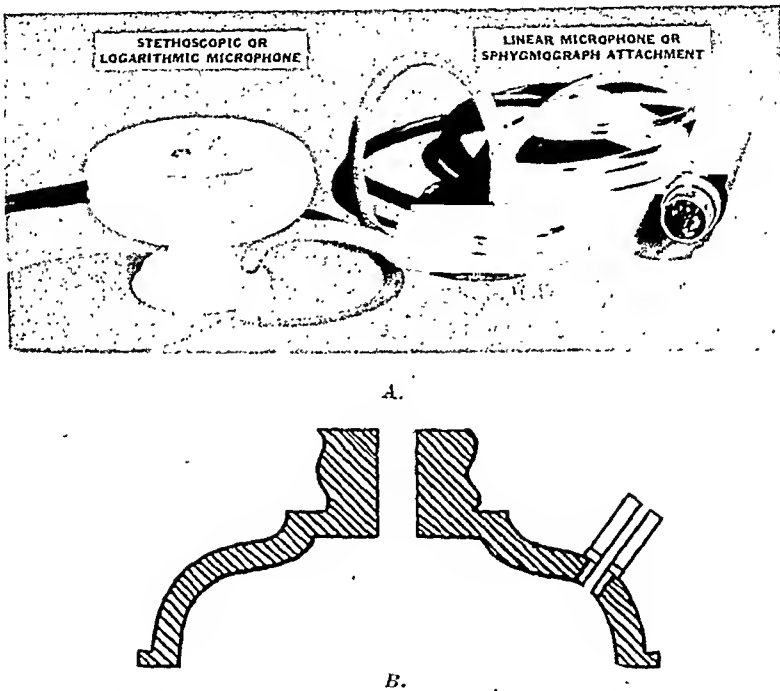


Fig. 6.—A, Arrangement for the simultaneous registration of the linear and stethoscopic or linear and logarithmic phonocardiograms. B, Cross-section view of chest piece. The chest piece was the large bell shown in Fig. 3.

An understanding of this principle is fundamental to the interpretation of all phonocardiograms. Briefly, it indicates that "loudness" and "intensity" are different factors, and that "loudness" is an auditory perception determined by "intensity" and "frequency." If we attempt, therefore, to record what the ear terms "loudness," we must distort our simple linear record by introducing the peculiar logarithmic response of human hearing and the specific distortion of the acoustic stethoscope.

Let us now compare the phonocardiograms taken on a normal person at the apex with the linear, stethoscopic, and logarithmic registration systems. Fig. 5A shows a simultaneous registration of the stethoscopic (upper) and linear (lower) phonocardiograms. Fig. 5B shows a simultaneous registration of the logarithmic (upper) and linear (lower) phonocardiograms.



Fig. 6 is a photograph of the chest piece employed for the simultaneous registration of the linear and stethoscopic, or linear and logarithmic, phonocardiograms. This chest piece employs a double outlet to two distinct types of microphones, and thus permits simultaneous registration on the same area of the chest.

The linear phonocardiogram of Fig. 5A and B may readily be recognized as the registration of the "apex beat" or "cardiogram." Wiggers' explanation<sup>25</sup> of the mechanism of the apex beat is: "During ventricular contraction, all diameters of the heart decrease; the base is pulled downward and the large vessels stretched, but the apex does not move upward. Owing to the spiral arrangement of the muscle fasciculi, the heart rotates to the right with the result that more of the left ventricular surface has a frontal exposure. Such rotation particularly affects the apex, the forward motion pressing it more firmly against the chest wall. This gives rise to the pulsation in the fifth intercostal space referred to as the apex beat. Records of this pulsation called cardiograms represent only heart movement."

The literature on the cardiogram is sparse; practically all the present day knowledge of the subject may be found in the works of Wiggers,<sup>25</sup> Frank,<sup>27</sup> Weitz,<sup>28</sup> Frank and Hess,<sup>29</sup> Weber,<sup>30</sup> Krönecker,<sup>31</sup> and Crehore.<sup>32</sup> Wiggers<sup>25</sup> states: "Optical tracings of the apex beat have so far been shown of value in only one respect, namely, that they incorporate the heart sounds and so allow an exact establishment of systole and diastole. According to Weber, they enable us to determine the beginnings of auricular systole, ventricular systole, systolic ejection and the opening of the A-V valves, and are further particularly valuable in determining the isometric contraction phase. It is quite obvious, however, that the same temporal relations may be established as well by the use of the optical venous and arterial pulses. Whether any other significance may be attached to pathological tracings, further investigation alone can determine. Weitz, it is true, has published a large series of optically recorded cardiograms both from normal individuals and from those with cardiac lesions. Aside from the addition of a variety of murmur vibrations associated with the particular lesions in question and the greater predominance of positive waves, they show nothing that can be regarded as distinctive, in a diagnostic sense."

Taquini, Massell, and Walsh<sup>33</sup> have recently shown the usefulness of the cardiogram in the differentiation between the opening snap of the mitral valve and the third heart sound when the isometric relaxation phase of the left ventricle is shortened in the presence of mitral regurgitation. The authors claim: "Under such circumstances, the third sound, which is produced during rapid inflow into the left ventricle, might not show its usual relation to the 'v' wave of the venous pulse, for the latter is associated with pressure changes in the right ventricle. Therefore, in order to ascertain the nature of the extra sound in these

eases, it is necessary to take the phonocardiogram simultaneously with the records of the apical pulsation."

*The Auricular Sound.*—By interrelating the linear, stethoscopic, and logarithmic phonocardiograms of Fig. 5A and B, we find that the cardiogram registers distinctly the auricular vibration or sound. The stethoscopic phonocardiogram shows a faint auricular vibration, and the logarithmic registration does not show any distinct vibrations which represent auricular contraction. In a considerable percentage of normal persons, the vibrational frequency of a transmitted auricular contraction is so low that it is incapable of passing through the average acoustic stethoscope. When such is the case, the stethoscopic phonocardiogram does not register the auricular sound. Human perception of such an auricular sound is an obvious impossibility with the added logarithmic attenuation. For the same reason, the logarithmic phonocardiogram will not register the auricular sound. The linear phonocardiogram is the only reliable phonocardiographic or auscultatory means of indicating the presence of a very low frequency auricular vibration. In phonocardiography, therefore, the cardiogram should prove useful as an indicator of the true location of the auricular contraction in the cardiac cycle.

*The First Heart Sound.*—In the apex cardiogram, the first heart sound is usually represented by a few coarse vibrations. The stethoscopic phonocardiogram on the same person shows somewhat similar, coarse vibrations, although attenuated, plus some superimposed, finer vibrations. The logarithmic phonocardiogram greatly attenuates the coarse vibrations and brings out a larger number of superimposed, finer vibrations.

Various investigators have shown that four factors are responsible for the production of the major vibrations which constitute the first heart sound. A discussion and bibliography on the subject may be found in the monograph by Orías and Braun-Menéndez.<sup>34</sup> The four factors are (1) the residual vibrations caused by auricular contraction—the auricular factor; (2) the muscular contraction and tension of the ventricular walls—the muscular factor; (3) the closure of the auriculoventricular valves—the valvular factor; and (4) the movements and distension caused by the ejection of blood from the ventricles into the arteries—the vascular factor; vibrations caused by opening of the semilunar valves initiate and fuse with this element of the first sound. In spite of conflicting experimental evidence, it appears likely that contraction of the ventricle produces vibrations in the absence of valve closure. These constitute the muscular factor and normally contribute to the early part of the first sound.

Caciro and Orías<sup>35</sup> have indicated that it is possible to distinguish four distinct components in the phonocardiographic representation of a normal first heart sound. Our observations confirm those of Caciro and

Orias. In Fig. 7, the four components may be distinguished in the stethoscopically registered phonocardiogram. The first component is a characteristically low frequency, or coarse, vibration which commences with the electrocardiographic QRS complex and normally precedes the apex of the wave. When an auricular sound is present, the first component usually merges with the auricular sound without a very definite interval. This phenomenon may be best seen in a linear phonocardiogram (Fig. 5A). The first component may thus be related to the auricular sound as a residual vibration, or the "auricular factor."

The vibrations which comprise the second component may be distinguished from the vibrations of the first component by their characteristically higher frequency and larger amplitude in a stethoscopically registered phonocardiogram. The second component always commences after the apex of the electrocardiographic QRS complex, and represents the beginning of the isometric, or presphygmie, phase of ventricular contraction. The second component records the closure of the mitral and tricuspid valves.

The third component is usually distinguishable from the second component (although it is of somewhat similar appearance) by a separation or slight splitting effect. The third component is synchronous with the opening of the semilunar valves and the onset of ventricular ejection.

The fourth component is composed of coarse vibrations which may extend to the peak of the "c" wave of the phlebogram or the anacrotic notch of a simultaneously registered central arterial pulse. Quite often the fourth phase vibrations terminate prior to, but rarely after, the peak of the "c" wave in a normal person. The vibrations which compose the fourth phase are thus believed to be caused by the acceleration of the blood in the arteries during the maximum ejection phase of ventricular systole.

In the linear phonocardiogram, there are always a preponderance of low frequency vibrations and a total or almost total lack of any of the higher frequency components that are so obviously registered in the stethoscopic and logarithmic phonocardiograms. A harmonic analysis of the frequency components of the first heart sound, which is a conglomeration of unrelated frequencies, shows that the coarse, or low frequency, vibrations are much greater in intensity than the higher frequency components. *The amplitude ratio of the major coarse and fine vibrations is so large that, when registered linearly, the fine vibrations are entirely lost or are, at best, insignificant. Thus, the linear phonocardiogram is extremely efficient in the registration of the first and fourth phases of the first heart sound and decidedly inefficient as an indicator of the second and third phases.*

The stethoscopic phonocardiogram attenuates the first and fourth phases and brings out distinctly the higher frequency second and third components. The reason the second and third components appear to be

of such magnitude in this type of registration is that more amplification is employed than is permissible in linear phonocardiography. If an equal amount of amplification were employed in linear phonocardiography, with the object of bringing out the second and third components, the deflections of the first and fourth components would be so large as to mask the second and third components. *It so happens that, with stethoscopic registration plus the additional amplification, the attenuation effects upon the first and fourth components are insufficient for obliteration, and sufficient to bring out clearly the second and third components.*

*Although the average acoustic stethoscope is capable of conducting the selectively attenuated four components of the first heart sound to the tympana of the ears, the observer is capable of hearing merely the higher frequency second and third components, and very little or practically none of the first and fourth components.* The reason human perception is so inefficient in the detection of the first and fourth components is that logarithmic hearing adds a still greater degree of selective attenuation. An interesting fact is that, at times, evidence of a first and fourth component may be present in the logarithmic phonocardiogram, but the observer, although extremely competent, will not hear the lower frequency vibrations because of the masking effects<sup>1</sup> of the apparently more intense second and third components upon the first and fourth.

Simultaneous registration of the stethoscopic or logarithmic phonocardiogram with the venous pulse may serve as a means of differentiating between a prolonged first heart sound and a first heart sound followed by a short systolic murmur. None of the four components of the first heart sound normally has a duration which allows it to extend beyond the peak of the venous pulse "c" wave. *Thus, it is reasonably safe to say that vibrations which extend beyond the peak of the "c" wave are the components of a systolic murmur.* On rare occasions, an extremely low frequency vibration may occur just after the peak of the "c" wave (during reduced ventricular ejection). Also, the fourth component vibrations are of a characteristically lower frequency than those of a systolic murmur, which also aids in the differentiation, even though the systolic murmur may commence early in the first heart sound, but not before the isometric contraction phase, i.e., the second component.

It should be of interest at this point to mention that a linear phonocardiograph is essentially an electrical sphygmograph.<sup>1, 59</sup> All the sphygmograms considered in this study were registered electrically or in accordance with linear phonocardiographic technique. Electrical sphygmography<sup>1</sup> possesses a number of inherent advantageous characteristics not readily obtainable with optical systems which employ the "Frank segment capsule" or any of its known modifications. A few of the more important characteristics are critical damping, high speed of response with ample sensitivity, good photographic definition because

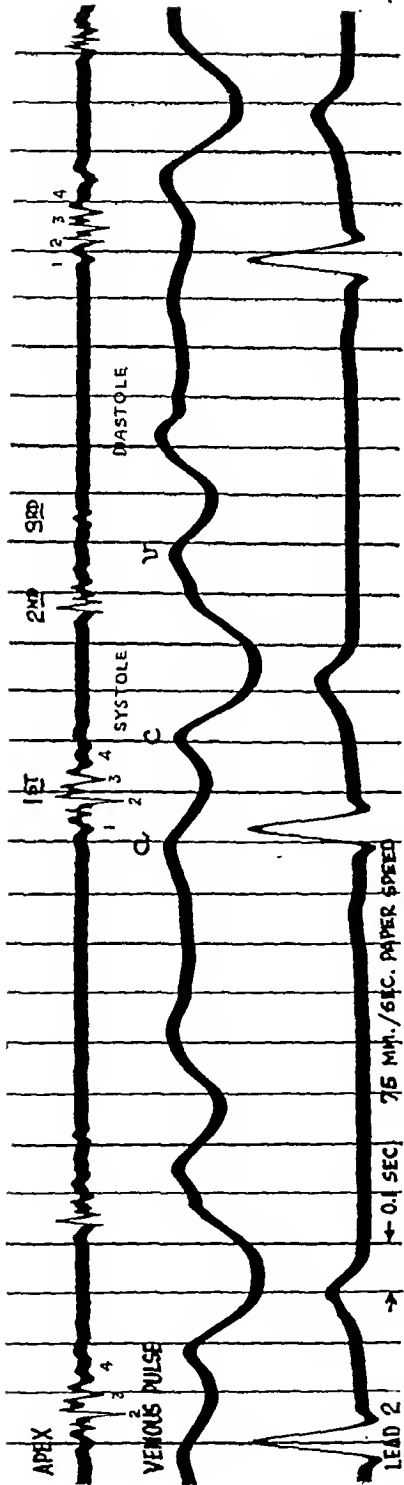


Fig. 7.—Simultaneous stethoscopic phonocardiogram, venous pulse, and electrocardiogram, to illustrate the relationship of the four components of the first heart sound.

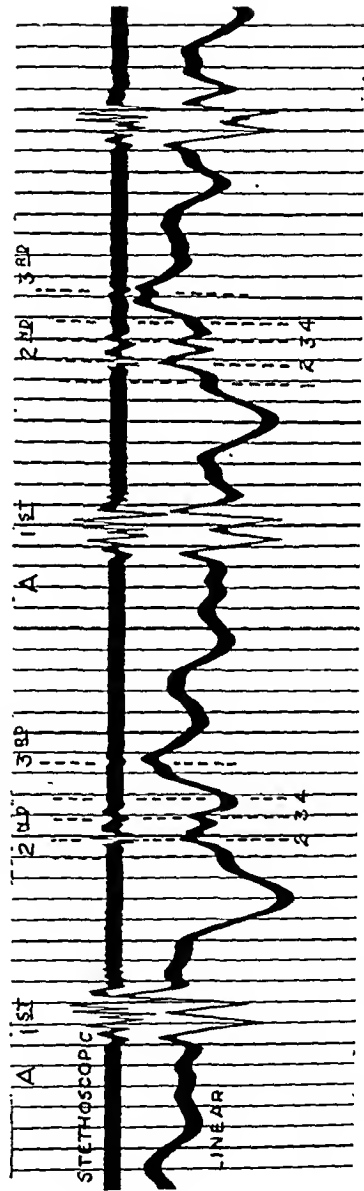


Fig. 8.—Simultaneous stethoscopic (upper) and linear (lower) phonocardiogram at the apex of a normal person. The four components of the second heart sound are present in the stethoscopic phonocardiogram, and their phase relationship to the apex beat is shown. A slight auricular vibration and the first and third heart sounds are distinctly registered.

of low optical magnification, simplicity of operation, automatic centering of the recording beam, adjustable sensitivity control, and non-deteriorating components. An important characteristic of the electrical sphygmograph attachment is that it may be used in an electrocardiographic channel (electronic type), and thus permits the registration of either an electrocardiographic lead or a sphygmogram.

Kountz, Gilson, Smith, and Edwards<sup>60-62</sup> have recently published "vibrograms" of the heart sounds with an apparatus which had a "drop off in transmission of less than 2 per cent between five cycles and fifteen hundred cycles per second." The authors give no figures for frequency response below five cycles per second. If the over-all response is linear from practically zero cycles per second, the apparatus is equivalent to our linear phonocardiograph and may be classified as a good sphygmograph. If the vibrograph response drops sharply below five cycles per second, it is no longer an accurate sphygmograph, but may be classified as a phonocardiograph which is linear between five cycles and 1,500 cycles per second.

*The Second Heart Sound.*—Billing,<sup>36</sup> in 1832, suggested that the second sound may be attributed to the closure of the semilunar valves. Rouanet,<sup>37</sup> in the same year, set up an experiment and verified Billing's theory. In 1882, Webster<sup>38</sup> suggested that additional sound vibrations may occur during this phase of the cardiac cycle as a result of arterial wall and blood column vibrations. The consensus at the present time favors these investigators.

Graphic analysis of a large number of phonocardiograms shows that the composite, normal, second heart sound, as recorded at the apex, is composed of four distinct components. The reason a composite of a large number of normal graphic registrations of the second heart sound is referred to in this analysis is that all four components do not always register distinctly in a single phonocardiogram. Fig. 8 shows a simultaneous stethoscopic (upper) and linear (lower) phonocardiogram, registered at the apex, in which the four components may be detected. In Fig. 9 there are additional records which show the four components of the second heart sound.

A composite linear phonocardiogram shows that the second heart sound commences with a small, subaudible vibration which we shall call the first component. The first component is quite distinct in the linear phonocardiogram of Fig. 8. This initial vibration is immediately followed by a few coarse vibrations—the second component. In Fig. 8 the second component is represented by a large, notched vibration. The second component is, in turn, followed by one or more very coarse vibrations which are usually of smaller intensity than those of the second component. In Fig. 8 the third component is represented by a single vibration. At the end of the third component, and simultaneous with the apex of the "v" wave of a venous pulse registration, a coarse vibra-

tion, or negative peak, terminates the second heart sound—the fourth component. In Fig. 8 the fourth component is represented by a notched, negative dip.

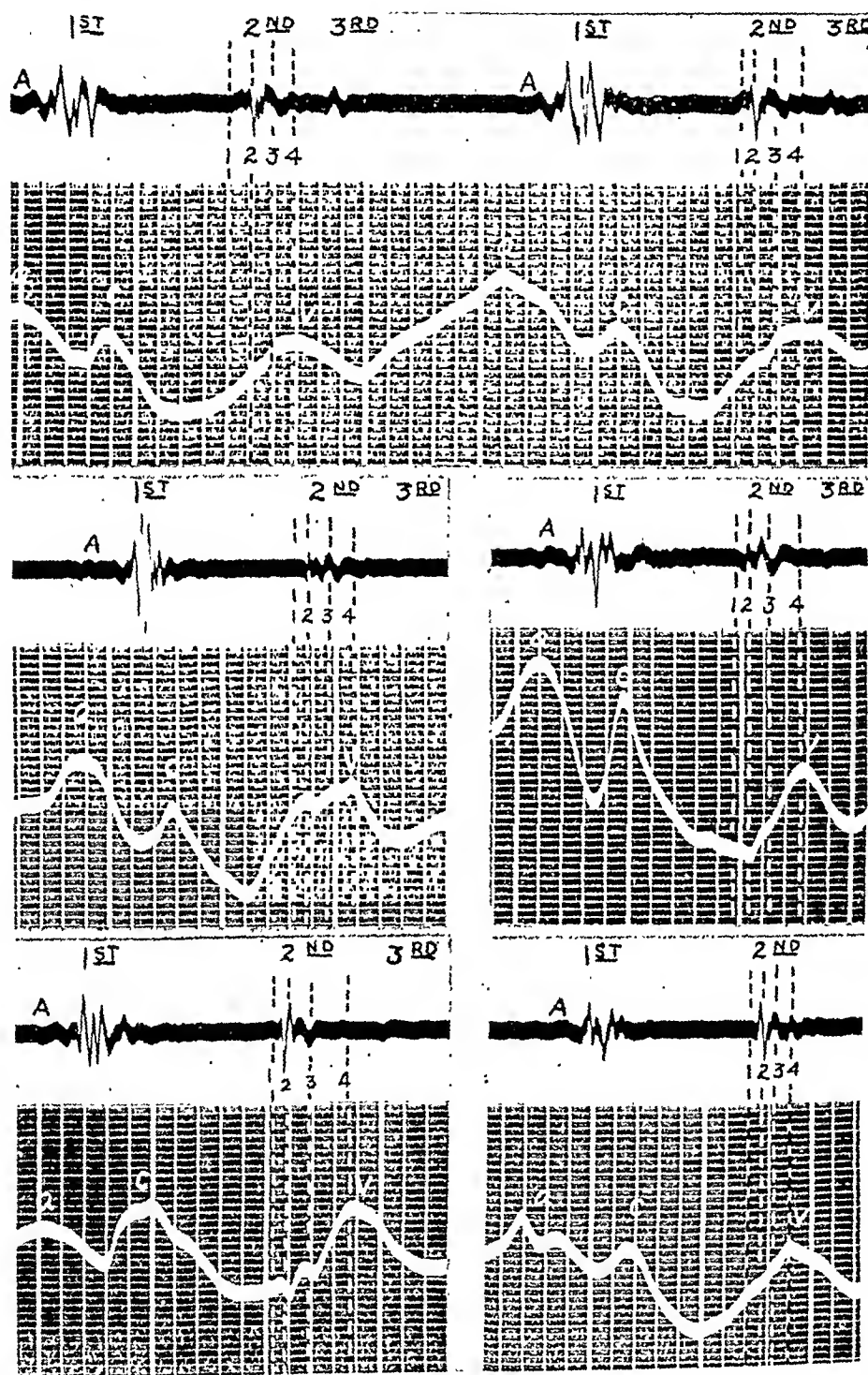


Fig. 9.—Simultaneous stethoscopic phonocardiograms at apex (upper) and phlebograms (lower) of five normal persons, showing the four components of the second heart sound and their relationship to the phlebogram. The auricular, first, and third heart sounds are also distinctly registered.

A composite, normal, stethoscopic phonocardiogram shows the first component of the second heart sound, but with some attenuation; this is well represented in Fig. 8. The first component is more distinct in some

of the records of Fig. 9. The second component is present, with the addition of superimposed higher frequency components; this is excellently illustrated by Fig. 8. The third component is present, but attenuated; Fig. 8 shows the third component distinctly. The fourth component is frequently present in a stethoscopic phonocardiogram, but considerably attenuated. In Fig. 8 a small wavelet representing the fourth component is noticeable.

A composite logarithmic phonocardiogram shows evidence of the presence of a first component of the second heart sound. The second component is present with more superimposed higher frequency components than appear in the composite stethoscopic phonocardiogram. The third and fourth components are usually completely eliminated.

The beginning of the second heart sound, or the first component, occurs at the beginning of the relaxation and diastolic fall of pressure in the ventricle. The second component vibrations may be ascribed to the closure of the semilunar valves. The vibrations that compose the second component contain many frequencies, in which the lowest predominate. This accounts for the introduction of higher frequency components in the stethoscopic phonocardiogram and still higher components in the logarithmic phonocardiogram at the expense of the lower frequency vibrations.

The third component of the second heart sound is probably caused by arterial wall and blood column vibrations. An additional source of vibration in this region may be the natural period vibration of the chest wall, which may be set into oscillation by the vibrations of the second component.

The fourth component vibration is the result of the opening of the mitral and tricuspid valves, as it always occurs simultaneously with the apex of the venous pulse "v" wave. The common occurrence of the fourth component in a considerable percentage of linear and stethoscopic phonocardiograms from normal persons, and its total absence in logarithmic phonocardiograms, indicate that the so-called "opening snap" is present in normal persons at a subaudible level. *Only in mitral stenosis does the fourth component become audible.*

In every normal phonocardiogram the train of vibrations which compose the four components of the second heart sound terminates with, or prior to, the occurrence of the simultaneously registered venous pulse "v" wave. Thus, a simultaneous phonocardiogram and phlebogram should supply sufficient data for the differentiation between a prolonged second heart sound and a second heart sound followed by a short diastolic murmur. *In other words, any vibrations which continue beyond the apex of the simultaneously registered venous pulse "v" wave are components of a diastolic murmur. This, of course, excludes the vibrations that may set up a third heart sound.*

*The Third Heart Sound.*—The generally accepted explanation of the cause of the third heart sound is well summed up by Orías and Braun-



Menéndez<sup>34</sup>: "The third heart sound is caused by vibrations of the ventricular walls due to their sudden distension by the inrush of blood from the auricles in the first moments of rapid ventricular filling." This third heart sound hypothesis, according to Orías and Braun-Menéndez, was first proposed by Ohm,<sup>39</sup> in 1921, and has been supported by Frey,<sup>40</sup> Lian,<sup>41, 42</sup> Gübergritz,<sup>43</sup> Melik-Gülnasarian,<sup>44</sup> Leonhardt,<sup>45</sup> Schütz,<sup>46</sup> and Braun-Menéndez and Orías.<sup>47</sup> Orías and Braun-Menéndez further state: "By the term 'ventricular walls' no distinction is implied between muscular and tendinous structures or valves. Furthermore, though this cause is stressed as the principal one, other subsidiary factors are not necessarily excluded. Some authors (Melik-Gülnasarian<sup>44</sup> and Routier and Van Bogaert<sup>48</sup>) stress the importance of an increased cardiac distensibility (diminution of tone) due to vagotonic disturbances in favouring the production of the sound."

Almost every linear phonocardiogram shows some evidence of a low frequency vibration which starts during the downslope of the simultaneously registered venous pulse "v" wave. In some normal persons a single positive vibration may be present, and, in others, two or possibly three such vibrations appear, but are of lesser intensity. The stethoscopic phonocardiogram usually shows the third heart sound as a single oscillation, but not so frequently or distinctly as does the linear phonocardiogram. The logarithmic phonocardiogram likewise registers a normal third heart sound as a single oscillation. Registration of a normal third heart sound is decidedly less frequent in a logarithmic phonocardiogram.

#### DURATION OF NORMAL HEART SOUNDS

*The First Heart Sound.*—Table I is a compilation of data found in the literature pertaining to the duration of the first heart sound in normal persons. The minimum normal duration of the first heart sound, as observed by Roos, is 0.041 second; whereas Strähl claims that it is 0.125 second—approximately a 3 to 1 ratio. Einthoven's measurement for maximum normal duration is 0.176 second; whereas Roos's is 0.064 second—a 2.75 to 1 ratio.

Differences in maximum and minimum measurements cannot be wholly attributed to the phonocardiographic method employed, such as direct versus electrical. As shown in Table I, among the authors who employed the direct method, Wiggers (0.05 sec.) and Strähl (0.125 sec.) showed the largest difference for minimum duration of the first heart sound—a 2.5 to 1 ratio. The largest difference for maximum duration of the first heart sound is between Strähl (0.175 sec.) and Ohm (0.097 sec.)—a 1.8 to 1 ratio.

Similar differences in measurement are found to exist among the investigators who employed the electrical phonocardiographic method. Einthoven obtained a minimum duration for the first heart sound of

0.058 second; whereas Kahn observed a minimum duration of 0.095 second—a ratio of 1.64 to 1. Einthoven obtained a maximum duration of 0.176 second; whereas Kahn's measurement was 0.109 second—a ratio of 1.62 to 1.

A comparison of the data obtained with Einthoven's electrical method and Wiggers' direct method indicates that they are in agreement within a reasonable percentage as to maximum and minimum duration.

TABLE I

COMPILATION OF DATA FOUND IN THE LITERATURE PERTAINING TO THE DURATION OF THE FIRST HEART SOUND IN NORMAL PERSONS

| AUTHOR                        | YEAR OF OBSERVATION | DURATION OF FIRST SOUND IN SECONDS | METHOD     |
|-------------------------------|---------------------|------------------------------------|------------|
| Einthoven, W. <sup>9</sup>    | 1907                | 0.058-0.176                        | Electrical |
| Roos, E. <sup>10</sup>        | 1908                | 0.041-0.064                        | Flame      |
| Weiss, O. <sup>11</sup>       | 1909                | 0.068                              | Direct     |
| Gerhartz, H. <sup>12</sup>    | 1911                | 0.11                               | Direct     |
| Kahn, R. H. <sup>13</sup>     | 1911                | 0.095-0.109                        | Electrical |
| Lilienstein <sup>14</sup>     | 1911                | 0.08                               | Electrical |
| Ohm, R. <sup>15</sup>         | 1912                | 0.083-0.097                        | Direct     |
| Eyster, W. <sup>16</sup>      | 1911                | 0.128                              | Electrical |
| Kapff <sup>17</sup>           | 1914                | 0.079-0.116                        | Direct     |
| Bridgman, E. W. <sup>18</sup> | 1915                | 0.145                              | Electrical |
| Strähl, E. O. <sup>19</sup>   | 1920                | 0.125-0.175                        | Direct     |
| Kanner, L. <sup>20</sup>      | 1921                | 0.16                               | Direct     |
| Wiggers, C. J. <sup>21</sup>  | 1923                | 0.05-0.152                         | Direct     |
| Schütz, E. <sup>22</sup>      | 1933                | 0.09-0.12                          | Electronic |
| Orias, O. <sup>23</sup>       | 1936                | 0.10-0.17                          | Direct     |
| Segura, A. S. <sup>24</sup>   | 1937                | 0.10-0.14                          | Direct     |

For analysis, we selected thirty-three normal, male, university students and made the following registrations at the apex with the subject in a supine position:

1. Stethoscopic phonocardiogram simultaneous with electrocardiographic Lead II.
2. Stethoscopic phonocardiogram simultaneous with the phlebogram.
3. Logarithmic phonocardiogram simultaneous with electrocardiographic Lead II.
4. Logarithmic phonocardiogram simultaneous with the phlebogram.

Table II shows our measurements of the duration of the first heart sound in the thirty-three normal persons. *The maximum duration of the first heart sound by the stethoscopic registration method was 0.165 second, as compared to 0.135 second by the logarithmic method. The minimum duration by the stethoscopic method was 0.105 second, and, by the logarithmic method, it was 0.08 second.*

*In every one of the thirty-three normal persons listed in Table II, the first heart sound was of longer duration in the stethoscopic phonocardiogram than it was in the logarithmic phonocardiogram. This difference in duration is due to the greater amount of attenuation that the first*

and fourth components are subjected to by the logarithmic registration system. We believe that herein lies the explanation for the divergent data of Table I. *In other words, lack of agreement as to the duration of the first heart sound is due primarily to dissimilar frequency response characteristics inherent in the phonocardiographs employed by the investigators.*

TABLE II

DURATION OF THE FIRST HEART SOUND IN THIRTY-THREE NORMAL PERSONS, MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

| SUBJECT<br>NUMBER | AGE<br>(YEARS) | DURATION OF FIRST SOUND (SECONDS) |             |
|-------------------|----------------|-----------------------------------|-------------|
|                   |                | STETHOSCOPIC                      | LOGARITHMIC |
| 1                 | 24             | 0.160                             | 0.120       |
| 2                 | 24             | 0.120                             | 0.090       |
| 3                 | 28             | 0.120                             | 0.090       |
| 4                 | 22             | 0.135                             | 0.120       |
| 5                 | 21             | 0.125                             | 0.105       |
| 6                 | 22             | 0.140                             | 0.120       |
| 7                 | 19             | 0.130                             | 0.100       |
| 8                 | 21             | 0.160                             | 0.115       |
| 9                 | 20             | 0.145                             | 0.125       |
| 10                | 26             | 0.105                             | 0.080       |
| 11                | 23             | 0.155                             | 0.125       |
| 12                | 24             | 0.105                             | 0.100       |
| 13                | 22             | 0.140                             | 0.115       |
| 14                | 22             | 0.120                             | 0.110       |
| 15                | 21             | 0.150                             | 0.115       |
| 16                | 22             | 0.110                             | 0.095       |
| 17                | 22             | 0.115                             | 0.080       |
| 18                | 21             | 0.110                             | 0.085       |
| 19                | 21             | 0.110                             | 0.090       |
| 20                | 22             | 0.150                             | 0.135       |
| 21                | 21             | 0.120                             | 0.090       |
| 22                | 20             | 0.115                             | 0.095       |
| 23                | 23             | 0.125                             | 0.100       |
| 24                | 22             | 0.165                             | 0.105       |
| 25                | 22             | 0.150                             | 0.120       |
| 26                | 21             | 0.130                             | 0.105       |
| 27                | 22             | 0.120                             | 0.110       |
| 28                | 22             | 0.140                             | 0.085       |
| 29                | 19             | 0.110                             | 0.100       |
| 30                | 23             | 0.110                             | 0.095       |
| 31                | 21             | 0.115                             | 0.105       |
| 32                | 38             | 0.115                             | 0.085       |
| 33                | 36             | 0.120                             | 0.085       |

We have shown that various types of chest pieces modify the frequency response of the phonocardiograph. The phonocardiograms summarized in Table II were registered with the 5-cm. diameter chest piece of Fig. 3. The reason such a large chest piece was employed is that it is highly efficient in the low frequency region where the normal heart sounds lie. Also, the application pressure<sup>1</sup> with such a chest piece is not critical. That is, the smaller the diameter of the chest piece, the more critical does the application pressure to the patient's chest become with respect to low frequency attenuation.

Smaller diameter chest pieces, and certainly the Bowles diaphragm types, attenuate the first and fourth components to a greater extent than

does the large, 5 cm. bell. It is thus obvious that more portions of the first and fourth components are lost in the phonocardiogram as the chest piece is decreased in diameter. The diaphragm chest piece attenuates these heart sound components most. In ascertaining the duration of the first heart sound, the investigators listed in Table I gave practically no consideration to this important characteristic.

The following are the factors, therefore, which may affect the duration of the first heart sound as detected at the surface of the chest: (1) Attenuation effects by the chest structure, (2) the frequency response characteristic of the phonocardiograph, and (3) the type of chest piece employed. (If small diameter chest pieces are used, the application pressure is an additional modifying factor.)

A number of investigators<sup>9, 11, 12, 14, 17-24</sup> have published figures on the frequency in cycles per second and the number of vibrations that compose the first heart sound. In our opinion, such figures are misleading and have very little meaning. For example, it has been shown that the four elements of the first heart sound have dissimilar frequency components. Under such conditions, how can such a complex train of waves be expressed with any accuracy by a single frequency value? Furthermore, the vibrational frequencies and the number of vibrations which compose the first heart sound are dependent upon the frequency response of the phonocardiograph and the type of chest piece employed. *To conclude, the first heart sound is a noise consisting of a conglomeration of unrelated frequencies that cannot be accurately regarded as a pure harmonic vibration, which many investigators have attempted to do.*

*The Second Heart Sound.*—Table III is a compilation of data by various authors on the duration of the normal second heart sound. The duration measurements of the second heart sound are as divergent as those published on the first heart sound.

Our measurements for the duration of the second heart sound in the thirty-three normal persons are given in Table IV. These measurements were made on the same stethoscopic and logarithmic phonocardiograms from which Table II was derived. *The maximum duration of the second heart sound by the stethoscopic registration method was 0.145 second, as compared to 0.110 second by the logarithmic method. The minimum duration by the stethoscopic method was 0.085 second, and, by the logarithmic method, 0.08 second.*

The data of Table IV again illustrate how the first, third, and fourth components of the second heart sound are more effectively attenuated in the logarithmic than in the stethoscopic phonocardiograms in such a way as to alter the measurable duration. Likewise, phonocardiographic data obtained with apparatus of dissimilar characteristics cannot be expected to correspond, as was true for the first heart sound.

*The second heart sound consists of a conglomeration of unrelated frequencies, as does the first heart sound. Therefore, the statement which*

TABLE III

COMPILATION OF DATA FOUND IN THE LITERATURE PERTAINING TO THE DURATION  
OF THE SECOND HEART SOUND IN NORMAL PERSONS

| AUTHOR   | YEAR OF<br>OBSERVATION | DURATION OF<br>SECOND SOUND<br>(SECONDS) | METHOD     |
|--|------------------------|--|------------|
| Einthoven, W. <sup>9</sup>                         | 1907                   | 0.041-0.104                              | Electrical |
| Roos, E. <sup>10</sup>                             | 1908                   | 0.045-0.048                              | Flame      |
| Weiss, O. <sup>49</sup>                            | 1910                   | 0.071                                    | Direct     |
| Gerhartz, H. <sup>12</sup>                         | 1911                   | 0.07                                     | Direct     |
| Kahn, R. H. <sup>13</sup>                          | 1911                   | 0.068-0.081                              | Electrical |
| Lilienstein <sup>14</sup>                          | 1911                   | 0.06                                     | Electrical |
| Ohm, R. <sup>15</sup>                              | 1912                   | 0.052-0.061                              | Direct     |
| Eyster, J. A. E. <sup>16</sup>                     | 1912                   | 0.095                                    | Electrical |
| Kapff <sup>17</sup>                                | 1914                   | 0.043-0.093                              | Direct     |
| Bridgman, E. W. <sup>18</sup>                      | 1915                   | 0.089                                    | Electrical |
| Strähl, E. O. <sup>19</sup>                        | 1920                   | 0.062-0.10                               | Direct     |
| Kanner, L. <sup>20</sup>                           | 1921                   | 0.10                                     | Direct     |
| Frey, W. <sup>50</sup>                             | 1926                   | 0.062-0.10                               | Electrical |
| Yoshioka, J. <sup>51, 52</sup>                     | 1932                   | 0.095-0.19                               | Electrical |
| Braun-Menéndez, E., and<br>Orías, O. <sup>53</sup> | 1934                   | 0.10-0.14                                | Direct     |

TABLE IV

DURATION OF THE SECOND HEART SOUND IN THIRTY-THREE NORMAL PERSONS,  
MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

| SUBJECT<br>NUMBER | AGE<br>(YEARS) | DURATION OF SECOND SOUND (SECONDS) |             |
|-------------------|----------------|------------------------------------|-------------|
|                   |                | STETHOSCOPIC                       | LOGARITHMIC |
| 1                 | 24             | 0.135                              | 0.105       |
| 2                 | 24             | 0.135                              | 0.090       |
| 3                 | 28             | 0.130                              | 0.065       |
| 4                 | 22             | 0.125                              | 0.090       |
| 5                 | 21             | 0.125                              | 0.100       |
| 6                 | 22             | 0.140                              | 0.105       |
| 7                 | 19             | 0.145                              | 0.080       |
| 8                 | 21             | 0.120                              | 0.085       |
| 9                 | 20             | 0.130                              | 0.070       |
| 10                | 26             | 0.135                              | 0.075       |
| 11                | 23             | 0.130                              | 0.080       |
| 12                | 24             | 0.125                              | 0.070       |
| 13                | 22             | 0.120                              | 0.080       |
| 14                | 22             | 0.110                              | 0.085       |
| 15                | 21             | 0.130                              | 0.110       |
| 16                | 22             | 0.100                              | 0.060       |
| 17                | 22             | 0.100                              | 0.070       |
| 18                | 21             | 0.105                              | 0.090       |
| 19                | 21             | 0.095                              | 0.075       |
| 20                | 22             | 0.135                              | 0.095       |
| 21                | 21             | 0.110                              | 0.090       |
| 22                | 20             | 0.125                              | 0.085       |
| 23                | 23             | 0.105                              | 0.065       |
| 24                | 22             | 0.130                              | 0.110       |
| 25                | 22             | 0.125                              | 0.075       |
| 26                | 21             | 0.115                              | 0.085       |
| 27                | 22             | 0.120                              | 0.100       |
| 28                | 22             | 0.125                              | 0.065       |
| 29                | 19             | 0.130                              | 0.110       |
| 30                | 23             | 0.095                              | 0.070       |
| 31                | 21             | 0.140                              | 0.105       |
| 32                | 38             | 0.115                              | 0.060       |
| 33                | 36             | 0.085                              | 0.055       |

we made with regard to measurements on the frequency in cycles per second and the number of component vibrations holds just as true for the second sound as it does for the first.

*The Third Heart Sound.*—The duration of the third heart sound was measured in the thirty-three normal stethoscopic and logarithmic phonocardiograms (Table V). The measurements in several of the normal curves are approximate because of the difficulty of accurately judging the start and end point of such a typically coarse vibration of low amplitude. *The maximum duration by the stethoscopic method was 0.085 second; and by the logarithmic method, 0.05 second. The minimum stethoscopic duration was 0.03 second, and the logarithmic minimum was 0.015 second.*

TABLE V

DURATION OF THE THIRD HEART SOUND IN THIRTY-THREE NORMAL PERSONS,  
MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

| SUBJECT<br>NUMBER | AGE<br>(YEARS) | DURATION OF THIRD SOUND (SECONDS) |             |
|-------------------|----------------|-----------------------------------|-------------|
|                   |                | STETHOSCOPIC                      | LOGARITHMIC |
| 1                 | 24             | 0.085                             | 0.035       |
| 2                 | 24             | 0.080                             | 0.020       |
| 3                 | 28             | 0.050                             | Not present |
| 4                 | 22             | 0.055                             | Not present |
| 5                 | 21             | 0.050                             | 0.050       |
| 6                 | 22             | 0.070                             | Not present |
| 7                 | 19             | 0.055                             | Not present |
| 8                 | 21             | 0.050                             | Not present |
| 9                 | 20             | 0.080                             | 0.025       |
| 10                | 26             | 0.060                             | Not present |
| 11                | 23             | 0.030                             | 0.015       |
| 12                | 24             | 0.045                             | Not present |
| 13                | 22             | 0.050                             | Not present |
| 14                | 22             | 0.065                             | 0.015       |
| 15                | 21             | Not present                       | Not present |
| 16                | 22             | Not present                       | Not present |
| 17                | 22             | 0.060                             | Not present |
| 18                | 21             | 0.040                             | 0.035       |
| 19                | 21             | 0.035                             | Not present |
| 20                | 22             | 0.055                             | 0.030       |
| 21                | 21             | Not present                       | Not present |
| 22                | 20             | 0.040                             | Not present |
| 23                | 23             | Not present                       | Not present |
| 24                | 22             | 0.065                             | 0.030       |
| 25                | 22             | Not present                       | Not present |
| 26                | 21             | 0.050                             | Not present |
| 27                | 22             | 0.040                             | Not present |
| 28                | 22             | 0.060                             | 0.045       |
| 29                | 19             | 0.055                             | Not present |
| 30                | 23             | 0.060                             | Not present |
| 31                | 21             | 0.055                             | Not present |
| 32                | 38             | 0.035                             | Not present |
| 33                | 36             | Not present                       | Not present |

*The third heart sound registered clearly in twenty-seven of the thirty-three stethoscopic phonocardiograms (85 per cent); whereas the logarithmic phonocardiograms showed a distinct third sound in ten of the normal persons (30 per cent).*

TABLE VI

INTERVAL BETWEEN THE BEGINNING OF THE SECOND HEART SOUND AND THE CENTER OF THE THIRD HEART SOUND IN THIRTY-THREE NORMAL PERSONS, MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

(There is no correlation between these intervals and the heart rate.)

| SUBJECT NUMBER | AGE (YEARS) | STETHOSCOPIC INTERVAL BETWEEN SECOND AND THIRD SOUNDS (SECONDS) | LOGARITHMIC INTERVAL BETWEEN SECOND AND THIRD SOUNDS (SECONDS) | HEART RATE PER MINUTE |
|----------------|-------------|---|--|-----------------------|
| 1              | 24          | 0.185   | 0.175  | 69                    |
| 2              | 24          | 0.180   | 0.160  | 78                    |
| 3              | 28          | 0.185   | Not present  | 75                    |
| 4              | 22          | 0.190   | Not present  | 60                    |
| 5              | 21          | 0.175   | 0.165  | 75                    |
| 6              | 22          | 0.205   | Not present  | 60                    |
| 7              | 19          | 0.190   | Not present.   | 68                    |
| 8              | 21          | 0.190   | Not present  | 54                    |
| 9              | 20          | 0.190   | 0.165  | 57                    |
| 10             | 26          | 0.180   | Not present  | 72                    |
| 11             | 23          | 0.180   | 0.175  | 66                    |
| 12             | 24          | 0.160   | Not present  | 84                    |
| 13             | 22          | 0.160   | Not present  | 68                    |
| 14             | 22          | 0.185   | 0.165  | 63                    |
| 15             | 21          | Not present   | Not present  | 66                    |
| 16             | 22          | Not present   | Not present  | 81                    |
| 17             | 22          | 0.160   | Not present  | 72                    |
| 18             | 21          | 0.170   | 0.160  | 72                    |
| 19             | 21          | 0.160   | Not present  | 66                    |
| 20             | 22          | 0.200   | 0.185  | 63                    |
| 21             | 21          | Not present   | Not present  | 78                    |
| 22             | 20          | 0.200   | Not present  | 75                    |
| 23             | 23          | Not present   | Not present  | 93                    |
| 24             | 22          | 0.195   | 0.170  | 63                    |
| 25             | 22          | Not present   | Not present  | 66                    |
| 26             | 21          | 0.185   | Not present  | 72                    |
| 27             | 22          | 0.165   | Not present  | 66                    |
| 28             | 22          | 0.180   | 0.160  | 78                    |
| 29             | 19          | 0.175   | Not present  | 75                    |
| 30             | 23          | 0.185   | Not present  | 69                    |
| 31             | 21          | 0.195   | Not present  | 57                    |
| 32             | 38          | 0.240   | Not present  | 96                    |
| 33             | 36          | Not present   | Not present  | 84                    |

Table VI gives the intervals between the beginning of the second heart sound and the midpoint of the third sound. The midpoint of the third sound was selected as a reference because it may be estimated with greater ease than the starting point. *The stethoscopic method showed a maximum interval of 0.240 second and a minimum of 0.160 second. The maximum logarithmic interval was 0.185 second, and the minimum, 0.160 second.* The interval difference between stethoscopic and logarithmic methods may be accounted for by the obliteration or attenuation of the first component of the second heart sound, which effectively shortens the interval. Obviously, phonocardiographs of dissimilar frequency response will not supply similar data. This is well illustrated by the values in Table VII.

*Miscellaneous Relationships.*—The amplitude ratio of the first to the second heart sound in the thirty-three normal apex phonocardiograms

TABLE VII

COMPILATION OF DATA FROM THE LITERATURE PERTAINING TO THE INTERVAL BETWEEN THE SECOND AND THIRD HEART SOUNDS

| AUTHOR  | YEAR OF OBSERVATION | INTERVAL BETWEEN SECOND AND THIRD SOUNDS (SECONDS) | METHOD     |
|---|---------------------|--|------------|
| Einthoven, W. <sup>9</sup>                                | 1907                | 0.13   | Electrical |
| Lewis, T. <sup>54, 55</sup>                               | 1913                | 0.18   | Electrical |
| Hess, O. <sup>56</sup>                                    | 1915                | 0.26   | Direct     |
| Bridgman, E. W. <sup>18</sup>                             | 1915                | 0.13-0.18  | Electrical |
| Leonhardt, W. <sup>45</sup>                               | 1932                | 0.115-0.15   | Electrical |
| Clerc, A., Zodac-Kahn, B., and Tavecchi, G. <sup>57</sup> | 1934                | 0.12-0.18  | Electrical |
| Braun-Menéndez, E., and Orías, O. <sup>53</sup>           | 1934                | 0.11-0.14  | Direct     |
| Duchosal, P. <sup>58</sup>                                | 1935                | 0.11-0.18  | Electrical |

TABLE VIII

AMPLITUDE RATIO OF FIRST HEART SOUND DIVIDED BY SECOND HEART SOUND IN THIRTY-THREE NORMAL STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

| SUBJECT NUMBER | AGE (YEARS) | STETHOSCOPIC AMPLITUDE (RATIO OF FIRST SOUND DIVIDED BY SECOND SOUND) | LOGARITHMIC AMPLITUDE (RATIO OF FIRST SOUND DIVIDED BY SECOND SOUND) |
|----------------|-------------|---|--|
| 1              | 24          | 1.30  | 0.93   |
| 2              | 24          | 1.43  | 1.10   |
| 3              | 28          | 1.43  | 1.16   |
| 4              | 22          | 1.45  | 1.00   |
| 5              | 21          | 0.92  | 1.00   |
| 6              | 22          | 1.00  | 1.06   |
| 7              | 19          | 1.20  | 0.67   |
| 8              | 21          | 0.71  | 1.00   |
| 9              | 20          | 1.04  | 0.92   |
| 10             | 26          | 1.27  | 1.27   |
| 11             | 23          | 0.78  | 0.84   |
| 12             | 24          | 1.00  | 0.68   |
| 13             | 22          | 0.85  | 0.75   |
| 14             | 22          | 1.44  | 0.92   |
| 15             | 21          | 0.83  | 0.70   |
| 16             | 22          | 0.90  | 0.62   |
| 17             | 22          | 1.00  | 0.75   |
| 18             | 21          | 0.94  | 1.11   |
| 19             | 21          | 0.66  | 0.75   |
| 20             | 22          | 1.00  | 2.00   |
| 21             | 21          | 0.93  | 0.77   |
| 22             | 20          | 0.67  | 0.59   |
| 23             | 23          | 1.00  | 1.13   |
| 24             | 22          | 1.11  | 0.88   |
| 25             | 22          | 1.07  | 1.00   |
| 26             | 21          | 0.91  | 0.91   |
| 27             | 22          | 1.04  | 1.43   |
| 28             | 22          | 1.18  | 1.19   |
| 29             | 19          | 1.20  | 1.20   |
| 30             | 23          | 1.00  | 0.54   |
| 31             | 21          | 0.72  | 0.73   |
| 32             | 38          | 1.00  | 1.09   |
| 33             | 36          | 0.71  | 0.64   |



is listed in Table VIII. *In twenty of the thirty-three normal stethoscopic phonocardiograms (60 per cent) the amplitude of the first heart sound was greater than, or equal to, that of the second sound. Fifteen of the logarithmic phonocardiograms (45 per cent) showed that the amplitude of the first sound was greater than, or equal to, that of the second.* This difference between stethoscopic and logarithmic registration may be explained by the greater preponderance of higher frequency components in the second sound than in the first. The relationship does not necessarily hold true for older persons.

*In nineteen of the thirty-three stethoscopic phonocardiograms (58 per cent), a slight trace of systolic murmur was present. The logarithmic registrations showed some evidence of a systolic murmur in twenty-eight of the thirty-three subjects (85 per cent). Furthermore, the logarithmic system registered the murmur whenever the stethoscopic system did.* This indicates that the selective attenuating properties which are peculiar to human hearing tend to bring out a slight murmur more efficiently because of the greater preponderance of high frequency components in such a murmur.

*The auricular sound was present in twenty-nine of the thirty-three stethoscopic phonocardiograms (88 per cent); whereas the logarithmic system registered it in seven of the thirty-three subjects (21 per cent).* This illustrates that human hearing is relatively inefficient in the detection of normal auricular sounds because of their low vibratory frequency.

#### SUMMARY AND CONCLUSIONS

1. When a patient is ausculted in the usual stethoscopic manner, the observer does not hear the cardiac vibrations as they actually exist at the source because of three major forms of modification, namely:

a. The heart sounds are altered in their transmission from the source to the surface of the chest.

b. The heart sounds that reach the surface of the chest are additionally modified by the acoustic stethoscope and the type of chest piece employed.

c. The observer does not perceive the heart sound vibrations as they are transmitted to the ears by the acoustic stethoscope.

2. The three major forms of cardiac sound modification are related to auscultation as follows:

a. The chest transmissional factor must be considered and handled as a variable quantity.

b. Modification effects that are introduced by acoustic stethoscopes and their chest pieces may be made nonvariable. No attempts at stethoscopic standardization have as yet been made. Until such standardizations are accomplished, the stethoscopic factor must be considered as a variable quantity in auscultation.

c. Modification effects that are introduced by average normal hearing may be considered as a constant quantity in auscultation, with the condition that personal factors, such as auscultatory experience, fatigue, surrounding noise level, and rhythmic concentration ability, are omitted.

3. The three major forms of cardiac sound modification that are encountered in auscultation may have the following relationships to phonocardiography:

a. In phonocardiography, as in auscultation, the chest factor must be considered as a variable quantity.

b. The modification effects that are introduced by an acoustic stethoscope and its chest pieces in auscultation may be reproduced perfectly by phonocardiography.

c. The logarithmic type of modification that is introduced in auscultation by average normal hearing may also be reproduced by phonocardiography.

4. Phonocardiographic registration may therefore be considered according to the degree of modification introduced, namely:

a. Linear phonocardiography, or the registration of the sound vibrations as they exist on the surface of the chest.

b. Stethoscopic phonocardiography, or the registration of the sound vibrations as they are transmitted to the ears by an average acoustic stethoscope.

c. Logarithmic (human audiographic) phonocardiography, or the registration of sound vibrations as they are perceived by a competent observer if the personal factors are omitted.

5. Linear, stethoscopic, and logarithmic phonocardiography are directly related to auscultation. Each phonocardiographic method is a representation of a definite stage of sound transmission in auscultation. Deviations may be introduced by a phonocardiograph with frequency response characteristics other than linear, stethoscopic, or logarithmic. Such deviations bear no direct relationship to the auscultatory transmission and detection stages. Therefore, a phonocardiograph with other than linear, stethoscopic, or logarithmic characteristics must be considered as either an apparatus of poor design or an expression of the designer's personal opinion, unless the deviation is based upon a natural constant.

6. The linear phonocardiograph is essentially an electrical sphygmograph which possesses several advantageous characteristics not common to the "segment capsule" or "direct optical" type of sphygmograph.

7. A linear phonocardiogram, when registered over the apex, is an "apex cardiogram," or "apex beat" tracing.

8. A chest piece was devised which makes possible simultaneous phonocardiographic registrations over the same precordial area. For example, this dual chest piece is useful for simultaneously registering the apex beat and the stethoscopic or logarithmic phonocardiogram at the apex.

Clinically, such simultaneous registrations may be useful in differentiating between the third heart sound and the opening snap of the mitral valve when the isometric relaxation phase of the left ventricle is shortened by mitral regurgitation. The apex cardiogram is also useful in timing diastolic events, as is venous pulse registration. In some persons it is rather difficult to record the venous pulse; in such cases, the apex cardiogram may be registered instead.

9. The first heart sound is composed of four components, namely:

- a. The first, which is caused by residual vibrations of auricular origin.
- b. The second, which is produced at the beginning of the isometric contraction phase of the cardiac cycle (closure of the mitral and tricuspid valves).
- c. The third, which is caused by the opening of the semilunar valves.
- d. The fourth, which is caused by the acceleration of the blood in the arterial vessels during the maximum ejection phase of ventricular systole.

10. The linear phonocardiograph is capable of registering the first and fourth components of the first heart sound efficiently, but is very inefficient in the registration of the second and third components.

11. The stethoscopic phonocardiograph registers the first and fourth components of the first heart sound with some attenuation, but does not obliterate the vibrations. The second and third components are registered distinctly.

12. The logarithmic phonocardiograph obliterates the first and fourth components of the first heart sound of most normal persons, and registers the second and third components distinctly.

13. When a normal person is ausculted, the observer rarely hears the first and fourth components of the first heart sound; the second and third components are well heard. Logarithmic hearing (as indicated by logarithmic phonocardiography) is responsible for this auscultatory condition because of the greater relative attenuation of the low frequency first and fourth components than of the higher frequency second and third components. Logarithmic attenuation of the first and fourth components is of sufficient magnitude to bring them below the level of human audibility.

14. A simultaneous stethoscopic or logarithmic phonocardiogram and venous pulse tracing may serve as a means of differentiating between a prolonged first heart sound and a first heart sound which is followed by a short systolic murmur. In the latter instance, it extends beyond the "c" wave peak.

15. Our observations indicate that the second normal heart sound may be composed of four components, namely:

- a. The first vibrations, which represent the beginning of the diastolic fall in pressure with ventricular relaxation.

b. The second group of vibrations, which are caused by the closure of the semilunar valves (termination of ventricular systole).

c. The third group, which are most likely due to the arterial wall and blood column vibrations. An additional, possible source of vibration in this phase of the second heart sound may be the natural period vibration of the chest wall, which may conceivably be set into oscillation by the second component.

d. The fourth component is caused by the opening of the mitral and tricuspid valves.

16. The logarithmic phonocardiogram almost always totally obliterates the first, third, and fourth components of the second heart sound vibrations, whereas the stethoscopic and linear phonocardiograms may show all four components. This indicates that no matter how competent an observer may be, he can hear only the second component of the second heart sound of a normal person because his hearing is logarithmic.

17. Although the duration of the normal second heart sound is nearly equal to that of the first, auscultation makes the second sound appear shorter. This is explained by the fact that, normally, two components are audible in the first heart sound, whereas only one is audible in the second heart sound.

18. A simultaneous phonocardiogram and venous pulse tracing may supply sufficient data for differentiating between a prolonged second heart sound and a second heart sound followed by a short diastolic murmur. In the latter instance, it extends beyond the "v" wave peak, but should not be confused with the vibrations of the normal third heart sound.

19. Stethoscopic and logarithmic phonocardiograms were taken on thirty-three normal university students. Our phonocardiographic measurements were compared with those in the literature. It must be realized that our data are limited to a narrow age group. For a complete study, similar data must be obtained from infancy to old age, and classified accordingly. Also, our phonocardiographic registrations were made only at the apex. A complete analysis should incorporate phonocardiograms at the pulmonic, aortic, and tricuspid areas, as well. However, this study was primarily intended to ascertain the causes of phonocardiographic divergences, and should be considered in this light. This study does indicate the causes of divergent phonocardiographic data in the literature. These are:

a. Nonstandardization of the over-all frequency response of the phonocardiograph.

b. Nonstandardization of the chest pieces.

20. Our observations on the thirty-three normal male students show that:

a. The maximum stethoscopic duration of the first heart sound is 0.165 second. The maximum logarithmic duration is 0.135 second.

b. The minimum stethoscopic duration of the first heart sound is 0.105 second. The minimum logarithmic duration is 0.08 second.

c. In every case, the stethoscopic duration of the first heart sound is longer than the logarithmic.

d. The maximum stethoscopic duration of the second heart sound is 0.145 second. The maximum logarithmic duration is 0.110 second.

e. The minimum stethoscopic duration of the second heart sound is 0.085 second. The minimum logarithmic duration is 0.08 second.

f. In every case, the stethoscopic duration of the second heart sound is longer than the logarithmic.

g. Inasmuch as the stethoscopic duration is longer than the logarithmic for both the first and second heart sounds, duration is a function of phonocardiographic frequency response.

h. The first and second heart sounds are noises composed of a conglomeration of unrelated frequencies. Therefore, it is incorrect to regard such sounds as one would a pure harmonic tone or vibration, which many investigators have attempted to do.

i. The maximum stethoscopic duration of the third heart sound is 0.085 second. The maximum logarithmic duration is 0.05 second.

j. The minimum stethoscopic duration of the third heart sound is 0.03 second. The minimum logarithmic duration is 0.015 second.

k. In every case, the stethoscopic duration of the third heart sound is equal to, or longer than, the logarithmic.

l. The third heart sound registered clearly in 85 per cent of the stethoscopic phonocardiograms, whereas it showed distinctly in 30 per cent of the logarithmic phonocardiograms. This indicates that a competent observer cannot detect a third heart sound as efficiently by auscultation as by stethoscopic phonocardiography.

m. Phonocardiographs of dissimilar over-all frequency response do not register the normal third heart sound with equal efficiency. The greater the low frequency attenuation, the less efficient is the phonocardiograph in the registration of the third heart sound.

n. The larger the diameter of the chest piece, the more efficient is the phonocardiograph as a detector of the third heart sound. A "Bowles" diaphragm type chest piece is extremely inefficient in the detection of the third heart sound. The same conditions hold true in auscultation when the acoustic stethoscope is employed.

o. The maximum stethoscopic interval between the beginning of the second heart sound and the midpoint of the third heart sound is 0.240 second; the logarithmic maximum is 0.185 second. The stethoscopic minimum interval is 0.160 second, and the logarithmic minimum is 0.160 second. The interval difference between stethoscopic and logarithmic methods may be accounted for by the logarithmic attenuation or obliteration effect upon the low frequency first component of the sec-

ond heart sound. Phonocardiographs of dissimilar over-all frequency response, therefore, cannot supply identical measurements of such a nature.

p. In 60 per cent of the stethoscopic phonocardiograms, the first heart sound registered with an amplitude greater than, or equal to, that of the second heart sound. The logarithmic phonocardiograms registered the first heart sound with greater or equal amplitude in 45 per cent of the cases. The logarithmic phonocardiograph, which registers the sounds as they are perceived by a competent observer, ausculting with an acoustic stethoscope at the apex, shows that, in the age group studied, the second heart sound is louder than, or as loud as, the first heart sound in 55 per cent of the cases.

q. In fifty-eight per cent of the stethoscopic phonocardiograms taken at the apex there was a slight trace of systolic murmur. Logarithmic phonocardiography shows a similar systolic murmur in 85 per cent of the cases. These figures indicate that the selective attenuating properties peculiar to human hearing tend to bring out this slight murmur with greater efficiency because of the greater preponderance of higher frequency components in the slight systolic murmur.

r. Eighty-eight per cent of the stethoscopic phonocardiograms registered an auricular sound, whereas the logarithmic phonocardiograms registered this low frequency sound distinctly in 21 per cent of the cases. Auscultation, therefore, is less efficient than stethoscopic phonocardiography as a means of detecting the auricular sound.

21. For maximum accuracy in all types of phonocardiographic analysis, a phonocardiograph capable of registering the heart sounds linearly, stethoscopically, and logarithmically should be employed.

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# OBSERVATIONS ON THE EFFECT OF TOURNIQUETS ON ACUTE CARDIAC CRISES, NORMAL SUBJECTS, AND CHRONIC HEART FAILURE

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DEATH from many forms of cardiac disease may be sudden. This is especially true of such conditions as acute myocardial infarction, paroxysmal left ventricular failure, and pulmonary embolism. It has long been recognized that, if one can tide the patient over the acute stage of the disease by minimizing the demands on the heart, and by the judicious use of supportive measures, his chances of recovery may be considerably enhanced. Acute failure of the left ventricle seems particularly amenable to treatment when it is promptly and vigorously applied. This depends not only on rest and drugs to improve myocardial function, but also, in many instances, on diminishing the work of the heart. It is well established that rapid lowering of venous pressure by phlebotomy<sup>1-6</sup> may produce pronounced relief of symptoms and rapid recovery of myocardial function in acute cardiac dyspnea. Indeed, phlebotomy has been hailed by some as a lifesaving procedure in left ventricular failure, especially when venous engorgement has developed.

It has been stated<sup>6</sup> that the improvement after bleeding is dependent in part on the sudden reduction of venous pressure, which facilitates recovery of the left ventricle and the establishment of a more adequate pulmonary circulation. To be effective, the lowering of venous pressure must be rapid. However, other factors may be involved because the blood volume after venesection may be quickly restored, and yet improvement may be maintained.

The efficacy of phlebotomy in many of these cases suggested to Danzer<sup>7</sup> that a similar effect might be obtained by the application of pneumatic tourniquets to the extremities, thus utilizing the peripheral venous system as a reservoir to decrease the circulating blood volume. His system employed a valve whereby the tourniquets could be inflated to any desired pressure. Danzer reported that this procedure produced a dramatic relief of symptoms in some cases of acute cardiac failure.

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Weiss and Robb<sup>8</sup> also applied tourniquets to the limbs in cases of acute left ventricular failure. They reported that this measure was more beneficial than phlebotomy from the standpoint of rapid relief of symptoms, although they thought the effects were of shorter duration. We have observed a number of persons with extreme pulmonary edema incident to sudden decompensation of the left side of the heart to whom pneumatic cuffs were applied (by a method described below). The dramatic relief of symptoms left no doubt as to the effectiveness of this procedure in such cases.

Certain advantages of this method over venesection seem to be self-evident. It would appear that more blood could be removed from circulation by utilizing the peripheral venous tree as a reservoir than would be desirable by bleeding alone. Another advantage is that a large quantity of blood may be retained "in storage" for a long period of time. There is the disadvantage that it does tend to cause venous dilatation, and thus might favor the production of venous thrombosis, and possibly emboli.

Acute myocardial infarction is another condition in which reduction of the quantity of blood flow to the heart might be beneficial as an adjunct to enforced rest and sedation in minimizing the demands on the myocardium. *Prima facie* consideration also suggests that the procedure might possibly be useful in cases of extensive pulmonary embolism and cor pulmonale, in which elimination of strain on the right ventricle is sought. Therefore, it seemed that the procedure merited further investigation, and an attempt was made to study the effect of peripheral venous congestion on normal persons and on patients with cardiac disease, with the hope of uncovering some of the physiologic factors which are responsible for the dramatic relief of left ventricular failure when tourniquets are used.

#### METHOD

The application of tourniquets to the extremities for long periods of time requires that they be released frequently to forestall damage to tissues. For these clinical and experimental observations an instrument\* was devised whereby the pneumatic cuffs could be rhythmically inflated and deflated in rotation; this permitted them to be retained in place for many hours without distress to the patient and without entailing the risk of tissue damage. Cuffs 3 inches wide were designed for use on the arms; those for the legs were 6 inches wide; the cuffs were of variable lengths so as to fit any size of limb. The tourniquets were applied as closely proximally as possible to each extremity, and were held in place by canvas straps. A small, double-acting pump maintained air pressure in a reservoir, whence the air was conveyed to the valves and cuffs. The valves were so arranged that the cuffs were kept inflated for four minutes, and were deflated, in rotation, for one minute; therefore, three were always inflated simultaneously. An escape valve on the reservoir could be adjusted to maintain a pressure (in mm. Hg) of any level in the cuffs. It was our custom to utilize the diastolic blood pressure level.

\*The instrument used in these experiments was built by the Burdick Corporation.

Studies were made on normal persons and on a group with heart disease. Two of the latter group, with typical signs of mitral stenosis, had hearts of essentially normal size. In the remainder (with hypertensive heart disease and coronary disease) the hearts were definitely enlarged.

Observations on cardiac size and the scope of ventricular motion were carried out by obtaining teleroentgenograms and roentgenkymograms on each patient immediately before the cuffs were applied, and again after they had been in operation for various lengths of time. Care was taken to see that the patient was as nearly as possible in the same position each time a roentgenogram was made, so that changes in heart size and the excursion of the ventricles could be more accurately evaluated.

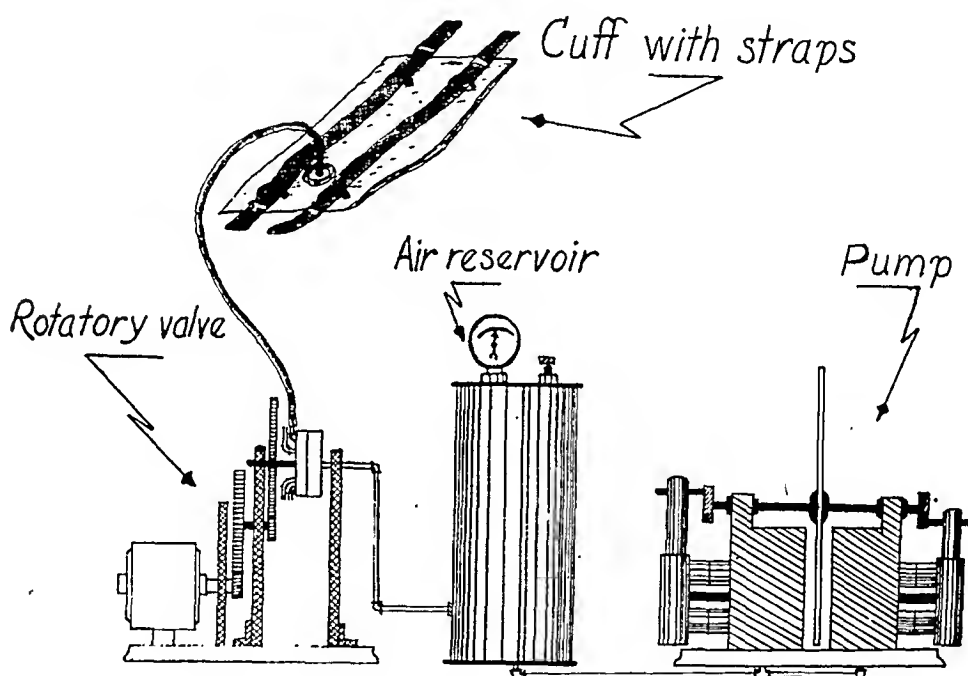


Fig. 1.—Schematic diagram of the instrument.

The arterial blood pressure was carefully measured after the patient had lain quietly and the pulse rate and blood pressure had become stabilized. This was repeated at intervals after application of the tourniquets. Venous pressures were measured with the apparatus described by Lyons, Kennedy, and Burwell.<sup>9</sup> The patient lay supine with the cuffs in place, and the venous pressure was measured in the femoral vein. The latter site for venepuncture was chosen because it enabled the arm cuffs to occupy their usual proximal positions; the cuff on the leg from which the pressure was recorded was placed just below Scarpa's triangle. With the patient lying supine, the level of the femoral veins was approximately the same as that of the right auricle, as shown by measurement.<sup>9</sup> A 3 per cent solution of sodium citrate was utilized in the manometer so that continuous readings could be made without trouble from clotting. The venous pressure was again noted after inflation of the tourniquets.

In a number of patients with normal hearts, both lateral and anteroposterior kymograms were obtained in order to estimate changes in the stroke volume of the heart before and after venous stasis was begun. This will be described in greater detail later.

## RESULTS

*Effect of Peripheral Venous Stasis on Venous Pressure.*—All of the subjects showed a decrease of venous tension after inflation of the tourniquets. The decrease, however, was gradual and had usually



Fig. 2.—A is a kymogram of a normal subject before the application of pneumatic tourniquets to the extremities. Note the dense parenchymatous lung markings adjacent to the right ventricle; this should not be construed as part of the heart shadow. B is the kymogram of the same person one-half hour after the tourniquets had been in place. Note the increased prominence of the right ventricular border.

reached the maximum point of fall in twenty to twenty-five minutes. This lower pressure was maintained and was not decreased further regardless of how long the procedure was continued. The degree of fall

varied from subject to subject and ranged from 3 to 10 cm. of water. When constriction of the limbs was discontinued, the venous tension gradually rose to its original level in five to eight minutes.

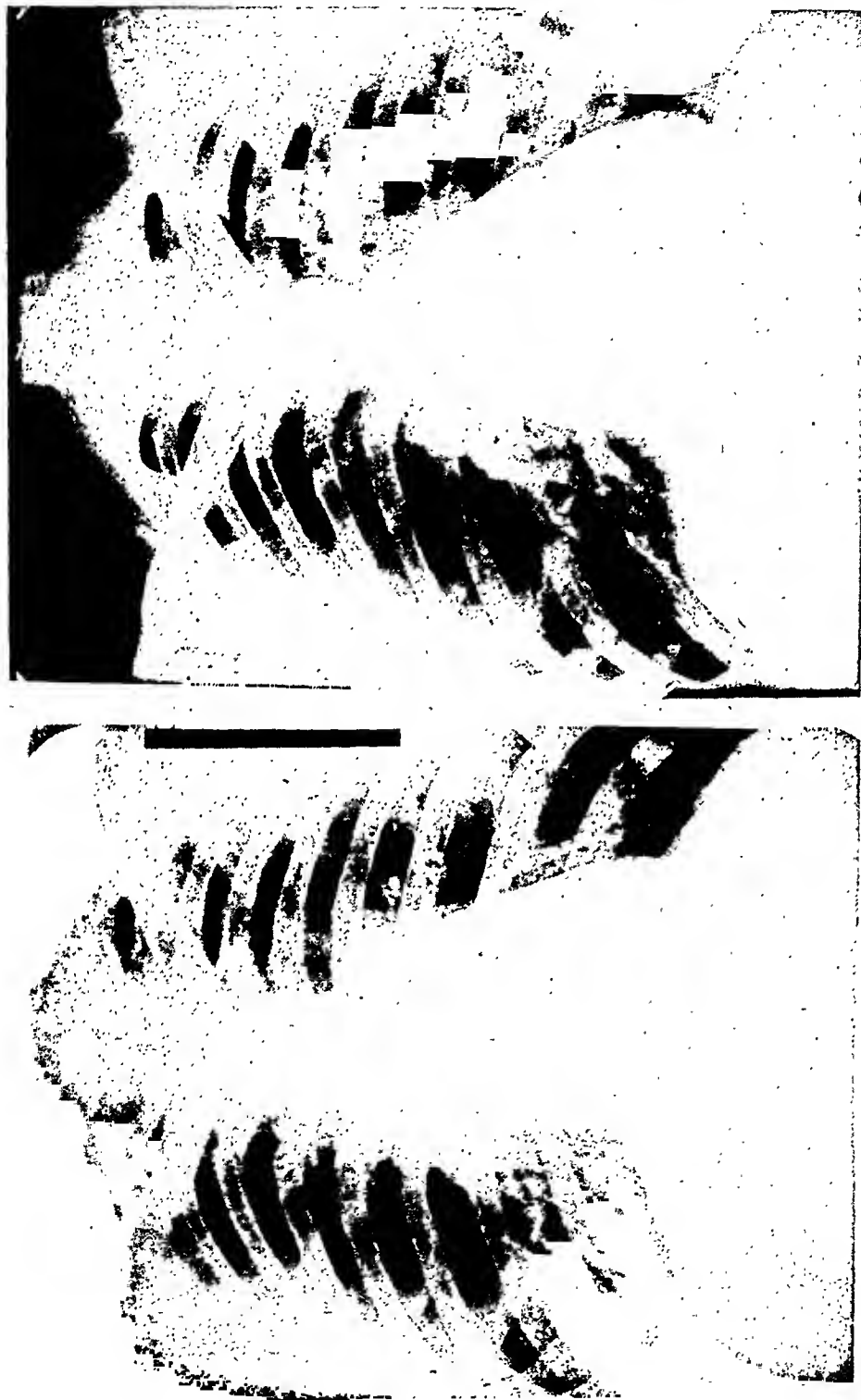


Fig. 3.—Patient with mitral stenosis; heart of normal size. The heart before (A) and one-half hour after (B) the pneumatic cuffs had been applied. In patients with mitral stenosis the apparent enlargement of the heart was greater during rhythmic venous congestion than in normal persons (see text).

*Effect on Arterial Blood Pressure.*—Constriction of the extremities of normal persons produced a slight rise of diastolic pressure (10 to 15 mm. Hg), but the systolic pressure was unchanged or somewhat reduced

(0 to 10 mm. Hg). These alterations in pressure were maintained constantly while the tourniquets were in operation; release of the cuffs resulted in prompt restoration of the original pressure level. Patients with blood pressures at hypertensive levels, on the other hand, reacted less uniformly. It seemed generally true that, in hypertension with definite (or marked) cardiac enlargement, the procedure caused a fall of blood pressure (10 to 20 mm. Hg systolic and diastolic); however, in some instances there was essentially no alteration. The pressure changes were maintained while venous congestion was in progress, and prompt restoration to the original blood pressure level occurred on release of the cuffs.

In persons with normal cardiovascular systems and in those with heart disease, *there was no alteration of pulse rate* during the time venous stasis was being maintained.

*Effect of Venous Stasis on the Size of the Heart Shadow and on the Contractions Recorded by Kymography.*—When the heart was of normal size, intermittent venous congestion resulted in *enlargement* of the cardiac silhouette. From a study of the roentgenograms, this enlargement apparently involved the right ventricle alone, the outline of which became conspicuous to the right of the sternum. There was no demonstrable alteration in the size or shape of the mediastinum or of the pulmonary conus. Of equal interest were changes in the kymograms. The excursions of the cardiac walls were definitely diminished by venous congestion. This appeared to be particularly pronounced in the left ventricle; the decrease in the wavelets of the right ventricle was definite, but less marked. No differences in the essential wave forms were noted in the control roentgenograms and in those taken after the tourniquets were inflated. In all of the cases, the roentgenograms were obtained one-half hour after venous congestion was begun, and those which were made later showed no progression of right ventricular enlargement or change in degree of myocardial motion. Essentially the same phenomenon was noted in the two cases of mitral stenosis, except that the enlargement of the heart after venous stasis was more pronounced. Table I illustrates the increase in size of the normal hearts.

TABLE I  
TRANSVERSE DIAMETERS OF HEARTS OF NORMAL SIZE

| CASE | BEFORE INTERMITTENT<br>VENOUS STASIS<br>(CM.) | AFTER $\frac{1}{2}$ HOUR OF INTER-<br>MITTENT VENOUS STASIS<br>(CM.) |
|------|---|--|
| 1    | 12.9  | 14.6   |
| 3    | 12.3  | 13.9   |
| 6    | 11.8  | 13.2   |
| 2*   | 12.6  | 19.6   |

\*Mitral stenosis (see Fig. 3).

In the cases of hypertension with cardiac enlargement, venous congestion usually produced *no* demonstrable change in the size of the heart;

however, in two instances the cardiac silhouette definitely decreased in size in all dimensions. Kymograms of these enlarged hearts showed a diminution in the amplitude of the movement of the ventricular walls (after establishing peripheral venous stasis with the cuffs), whether the

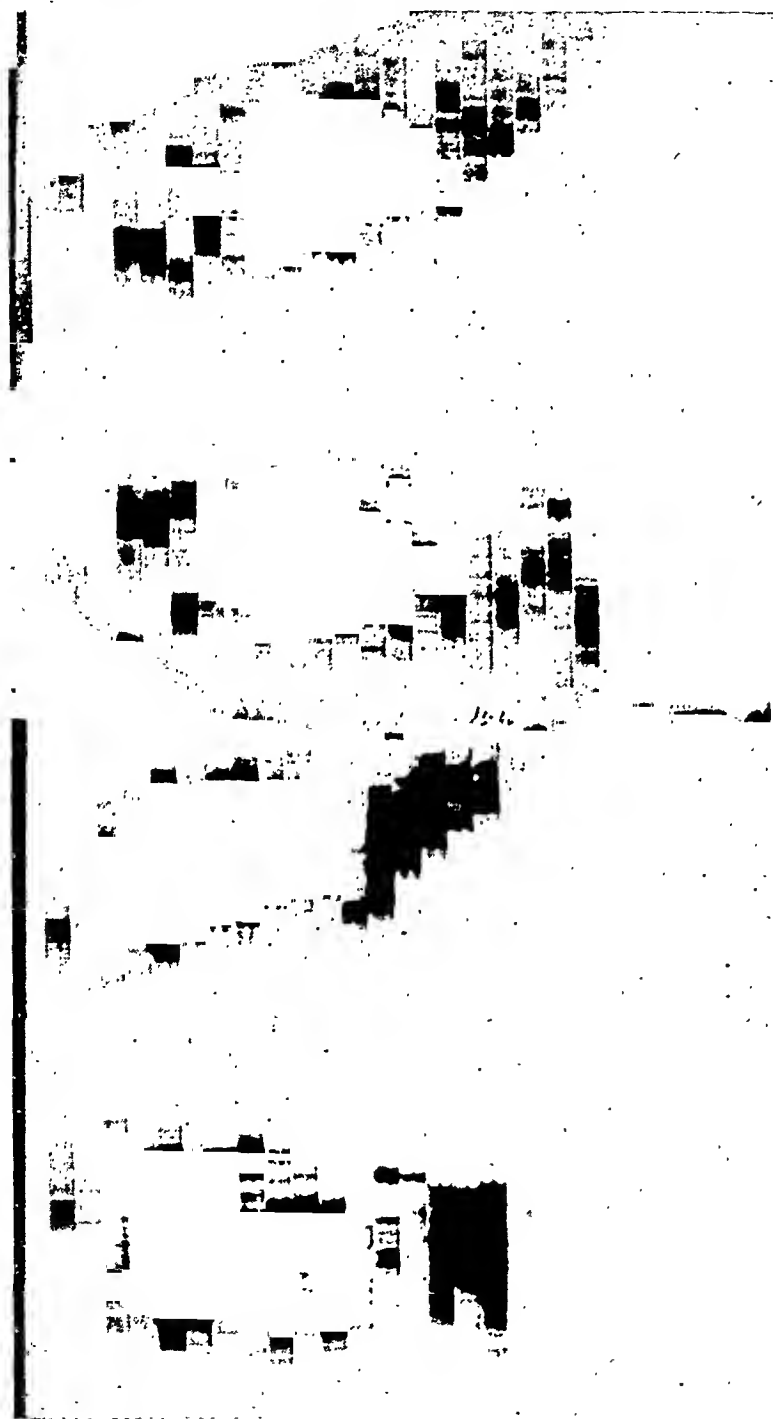


Fig. 4.—Kymograms of patient with hypertensive heart disease with moderate cardiac enlargement. The heart before (A) and after (B) inflation of the cuffs for one-half hour. There was no essential change in the size of the heart. Note the diminution in the excursions of the heart wall (B).

heart became smaller or not. Nevertheless, the fine patterns of the movements were preserved. In these cases, the diminution of motion appeared to involve the right and left ventricles equally.

The diminution in the excursion of the heart walls made it seem that cardiac output had been reduced. An attempt was therefore made to

estimate the change in cardiac output by means of kymography. Ungerleider and Gubner<sup>11</sup> have recently reviewed the formulas suggested for the estimation of heart volume by measuring certain diameters of the heart in systole and diastole. We utilized the Benedetti formula,



Fig. 5.—Kymograms of a patient with essential hypertension and angina pectoris. After application of the tourniquets (*B*) for one-half hour, the heart was somewhat smaller; the amplitude of the crests and troughs was diminished.

as outlined by them, in studying a group of normal persons to whom the pneumatic cuffs were applied. The details of the procedure need not be repeated here. We are aware that the exactness of our figures may be open to question, because repeated examination of the same per-



son introduced a probable error of position. However, it was found that the estimated output of the heart fell from 25 to 45 per cent after the establishment of venous stasis. That the cardiac output was diminished would seem to be borne out by the fact that a lowering of venous pressure and a diminution in the peaks and troughs in the kymograms occurred without any change in heart rate as blood was held stagnant in the extremities.

*Venous Stasis and Improvement in Symptoms.*—In some of the cases of marked cardiac enlargement the patients were being treated with digitalis, although their myocardial reserve was so diminished that they suffered from mild dyspnea even at rest, and some had orthopnea. All of them exhibited some signs of pulmonary congestion (a few sibilant and moist râles at the bases of the lungs). During a half-hour period after application of the cuffs, these patients insisted that their shortness of breath disappeared and that they could lie flat without distress. Examination of the chest showed that the signs of congestion were greatly reduced. This improvement was maintained over a period of several hours after the cuffs were removed. In view of the fact that great improvement may be obtained in cases of acute cardiac dyspnea by this method, as noted by Weiss and Robb and by us, it was not surprising that milder pulmonary edema was also benefited.

In a group of cases of acute left ventricular decompensation and pulmonary edema, we noted marked improvement as a result of this procedure. Complicating factors (pneumonia) ultimately caused death in two of eight patients who were studied. In a study of ten patients with acute myocardial infarction, this treatment was given for a period of fourteen days. All of them survived, whereas the mortality rate of such patients, in a hospital from which a similar group of patients was chosen, was 37 per cent. A more detailed study must be made before definite conclusions can be drawn, but these results suggest that this treatment affords some protection to the heart when the function of the *left* ventricle is impaired.

On the other hand, two patients with massive pulmonary embolism were definitely not benefited by the treatment. Both died soon after application of the cuffs. This seemed also to be true of chronic right ventricular disease. Three patients with cor pulmonale caused by pulmonary fibrosis were not improved by intermittent venous stasis.

#### DISCUSSION

The mechanisms which govern the responses of the cardiovascular system as a whole are so interdependent that it is difficult to separate them. In the evaluation of these experimental data a multitude of factors must be considered, and, in the light of present knowledge, only a suggestion of the meaning of the phenomena can be offered.

A reduction of venous pressure occurred in all of the subjects (proximal to the cuffs) during superficial constriction of the limbs. One would expect this to occur because a large volume of blood may be trapped in the peripheral venous system. Although inflation and deflation of the cuffs in rotation allowed blood to be held in three extremities simultaneously, the quantity of inactive blood was not strictly constant because of the differences in volume of the upper and lower extremities. However, it is possible that as much as an eighth of the total circulating blood volume was impounded.

It seems clear that, in normal subjects, intermittent constriction of the four limbs results in enlargement of the cardiac silhouette. Whether or not the enlargement is limited to the right ventricle, as one might surmise from study of the roentgenograms, is difficult to say. It is possible that both chambers may be increased in size, but that the right is more affected than the left. The work of Eyster and Middleton<sup>12</sup> would lead one to expect that the opposite takes place. These observers noted that the cardiac silhouette decreased in size in donors who were bled an estimated 8 per cent of the total blood volume.

The explanation of cardiac enlargement during intermittent venous congestion of the limbs does not appear to be simple; however, a number of possibilities deserve consideration.

Since our procedure had an obvious physical effect on the vascular system, one might surmise that some change may have occurred which produced overfilling of the ventricles. A second possibility is a disturbance in the nervous relationship which would reflexly stimulate the cardiac nerves and produce cardiac dilatation. The third, and perhaps most likely, explanation is that the physical obstruction leads to the production of chemical factors in the body which are carried by the blood to the heart and cause myocardial dilatation.

*The Physical Effect of Cuffs.*—The effect of the application of cuffs is to reduce the amount of blood flowing to the heart. This was shown by Ebert and Stead,<sup>10</sup> who demonstrated that as much as one-sixth to one-eighth of the total amount of blood may be impounded in the extremities when they are constricted by tourniquets. Our experiments have verified the fact that as much as one-eighth of the total volume of blood may be held in the periphery. In our studies a decrease in the systemic venous pressure was noted on application of the cuffs. This might indicate that there was a reduced amount of blood flowing to the heart. It would appear logical that the physical effect of the cuffs on the circulating blood volume was not a factor in increasing the size of the heart. The irregularity in the amount of blood returning to the heart (because of the difference in volume of the extremities) would not seem to be a factor in cardiac dilatation because of the small amount of blood that was released at any one time. There was only a slight fluctuation of venous pressure when the individual cuffs were released.

*The Influences of Venous Congestion on Cardiac Reflexes.*—A reflex mechanism as the cause of the increase in cardiac size appears unlikely. Under the circumstances of our studies it seemed possible at first that the high peripheral pressure in the extremities might have caused cardiac dilatation through reflex vagal stimulation. If such were the case, certainly one would expect other evidence of vagal stimulation, such as slowing of the heart rate. However, the heart rates remained fairly constant when the cuffs were in place.

*The Chemical Influence of Blood From Congested Extremities.*—A chemical factor as a possible cause of the increase in heart size must be considered. It was interesting that persons who had heart disease (that is, cardiac hypertrophy and dilatation) showed no increase, and frequently a decrease, in cardiac size. Since these patients had heart failure, and many of them showed a slight increase in venous pressure, one might consider that their hearts were already exposed to some factor which was associated with venous congestion. In these cases the application of the cuffs simply produced a mechanical effect by decreasing the amount of blood flowing to the heart and reducing cardiac size and work, and did not increase the size of the cardiac silhouette because of the mild venous congestion which was already present. If such an assumption were true, it would seem to indicate that, in patients with chronic congestive heart failure, there may be a substance in the circulation which causes the heart to dilate.

Normal persons, and those with heart disease without peripheral congestion, responded by an increase in cardiac size. The subjects whose cardiac shadow increased to the greatest extent with application of the cuffs were those whose cardiac size increased maximally during exercise. These subjects had mitral stenosis and always developed increased venous pressure with exercise. These observations were so uniform and persistent that they suggested that the same factor which caused cardiac dilatation with exercise likewise produced it when the cuffs were in place. Since there was just one common condition under both circumstances, that is, peripheral venous congestion, it would seem that this might be the factor. If this were true, a new conception of the cause of cardiac dilatation would be introduced. Increased venous pressure is the primary factor.

It is usually stated that the cause of pathologic cardiac dilatation is an increased load on the myocardium or weakening of the cardiac muscle. Neither of these factors could have been of primary importance in these cases when the cuffs were in place. These studies suggest that peripheral venous congestion produces cardiac dilatation when the blood returns to the heart. The persistence of the changes in each case that we have studied indicates to us that we are dealing with an important cardiovascular mechanism which seems not to have been considered heretofore.

The application of tourniquets to patients with primary right ventricular failure or acute cor pulmonale caused by extensive pulmonary embolus appears to be contraindicated. This would apply to cuffs which are inflated and deflated in rotation, as well as to tourniquets which are tightened all together and held so. An explanation for this is suggested by the work of Fineberg and Wiggers,<sup>13</sup> namely, that, in primary right ventricular failure, a drastic reduction of venous pressure may increase the degree of failure by further diminishing the force of right ventricular contraction, with the result that the right ventricle becomes less able to overcome the resistance of the pulmonary bed.

#### SUMMARY

1. The application of tourniquets to the extremities of patients with paroxysmal left ventricular failure usually results in dramatic improvement.

2. This procedure was further investigated by means of an instrument which inflated and deflated cuffs, placed on the arms and thighs, in rotation. The effects on venous and arterial pressure, on cardiac size and contraction, and on cardiac output were observed in normal persons and in patients with heart disease. In both groups, rhythmic inflation of the cuffs caused a fall in venous pressure, diminution of cardiac contraction, and a fall in cardiac output; the arterial pressures were essentially unchanged. In normal persons some enlargement of the heart occurred during rhythmic constriction of the extremities; in patients with hypertensive heart disease the size of the heart usually remained unchanged, but, in two instances, the heart diminished slightly in size. A suggestion as to the cause of these phenomena is offered.

3. It is suggested that this procedure may be useful in the treatment of acute myocardial infarction, as well as in paroxysmal cardiac dyspnea. It appears to be of no benefit in right ventricular failure.

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#### DISCUSSION

DR. WILLIAM S. COLLENS, Brooklyn, N. Y.—I should like to congratulate the authors, and wish to say that Dr. Shapiro, in our clinic, recently conducted the same kind of studies and came to the same conclusions. He used the apparatus which we devised for intermittent venous occlusion, and modified it by attaching four cuffs to it. Three cuffs were inflated at one time while one cuff was deflated in sequence.

DR. WILLIAM B. KOUNTZ.—The method was devised primarily as a technique in reducing cardiac activity, or work. We were very much interested to note that, in left ventricular failure, one not infrequently found that the patient was greatly improved. We extended this to a group of patients who had coronary thrombosis. We had a rather nice control series, because the group was chiefly at the city infirmary, where about 26 per cent of all patients with coronary thrombosis died soon after the shock of coronary occlusion. By using this technique, we found that we could reduce that mortality considerably.

# THE INFLUENCE OF XANTHINE DRUGS AND ATROPINE ON THE MORTALITY RATE AFTER EXPERIMENTAL OCCLUSION OF A CORONARY ARTERY

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THERE is still considerable difference of opinion among clinicians concerning the value of the xanthine drugs, theobromine and theophylline, in the treatment of diseases of the coronary arteries and angina pectoris. With respect to the latter, reports have been published recently by Gilbert and Kerr,<sup>1</sup> Brown and Riseman,<sup>2</sup> Massel,<sup>3</sup> Levy and his associates,<sup>4</sup> and LeRoy<sup>5</sup> which strongly advocate the use of these drugs. On the other hand, Master, Jaffe, and Dack<sup>6</sup> and Gold and his associates<sup>7</sup> believe that these same drugs are of little or no value in the management of angina pectoris. In the standard textbooks of medicine one finds the same divergence of opinion. Less has been published recently about the use of these agents in the early treatment of acute myocardial infarction caused by occlusion of a coronary artery. Just as in the discussions of angina pectoris, the textbooks express discordant views about the use of these drugs after myocardial infarction. In fact, some of the books, and some clinicians, foster the impression that, since the blood flow is completely interrupted by coronary occlusion, there is no rationale for the use of vasodilating agents. The experimental literature is scanty and is not of one accord. Gold and his associates<sup>8</sup> have published evidence which demonstrates that the xanthines are of no value. Fowler, Hurevitz, and Smith,<sup>9a</sup> however, reported striking benefits in their series of experiments. It is obvious that, if the rationale for the use of the xanthines in angina pectoris is the ability of these drugs to augment the coronary blood flow, they should be of equal or greater value in the treatment of acute myocardial infarction. Recent anatomic studies<sup>10</sup> of coronary occlusion and myocardial infarction have disclosed the fact that, in 40 per cent of the cases of infarction, the closure of the coronary artery was not complete. Such patients certainly should be helped by drugs that decrease the peripheral resistance in the coronary circulation. Studies by Hall and his associates<sup>11</sup> suggest another very important theoretical reason for the administration of drugs which are capable of augmenting the coronary blood flow in cases of recent infarction of the myocardium. They showed that the mortality rate after experimental occlusion of a coronary artery in dogs may be strikingly modified by

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eardiosensory denervation. In their conscious animals there was a 75 per cent mortality after ligation of the circumflex branch of the left coronary artery. Bilateral stellate ganglionectomy and upper thoracic sympathectomy reduced this rate to 25 per cent. It was their opinion that a myocardial infarct acted as a stimulus to a reflex whose afferent portion was the eardiosensory nerves, whose efferent portion was the vagus nerves, and whose effect was a reflex constriction of the coronary arteries supplying the uninfarcted myocardium. In all of their experiments, death, when it was observed, was due to ventricular fibrillation, which was induced in part, or entirely, they believe, by generalized myocardial ischemia caused by the reflex coronary vasoconstriction. This hypothesis has been corroborated in three ways by work done in our laboratory: (1) In colored motion pictures of a dog's heart, taken during and immediately after coronary ligation, a definite darkening of the color of the uninfarcted myocardium can be clearly seen just before the onset of ventricular fibrillation.<sup>12</sup> (2) In a report to be published soon, one of us (G. V. L.) has demonstrated that, in conscious dogs, there is a periodic decrease in the blood flow through the circumflex branch of the left coronary artery shortly after occlusion of the anterior descending branch. (3) Finally, in the present report, we shall show that drugs which are known to cause coronary vasodilatation in the dog have practically the same influence on the mortality rate after coronary occlusion as does eardiosensory denervation.

Our position in regard to the use of the xanthine drugs in the treatment of myocardial infarction may be stated briefly as follows:

1. After occlusion of one coronary artery, reflex vagal vasoconstriction of the arteries in the uninfarcted myocardium occurs, and the resulting ischemia is responsible for the early, sudden death of victims of myocardial infarction.

2. Certain drugs decrease the mortality rate in dogs after experimental coronary occlusion.

3. These drugs are known to be capable of increasing the coronary blood flow.

4. Therefore, they influence the mortality rate by augmenting the coronary flow and preventing the general ischemia of the myocardium which may occur reflexly after coronary occlusion.

5. Since these drugs do this, they are useful in the treatment of acute myocardial infarction and angina pectoris.

Throughout this paper, the phrase "mortality rate" has a special meaning. To make our data comparable to those of Hall, et al.,<sup>11</sup> we classify as sudden or reflex deaths those that occur within twenty-four hours after coronary occlusion. Only these deaths are counted in the calculation of the mortality rate. When this is done, the mortality rate after performing coronary occlusion upon anesthetized animals varies from 25 per cent to 100 per cent. Since the chief factor in the causation

of this type of sudden death is reflex vagal vasoconstriction, the depth and the nature of the anesthesia are important. McEachern, Manning, and Hall<sup>11</sup> reported a mortality rate of 75 per cent after producing coronary occlusion in conscious dogs. In our laboratory the rate after a similar procedure was 70 per cent. Because the suffering of a conscious dog with a myocardial infarct is often distressing and disturbing, we sought an anesthetic technique which, by preserving autonomic reflex activity, would yield the same mortality rate. The morphine-nembutal anesthesia that we now use does this.

The experimental procedure is as follows: One-half hour before operation, morphine sulfate in the amount of 1.0 mg. per kilogram is given subcutaneously to healthy dogs. Fifteen minutes later a solution of nembutal (60 mg. per cubic centimeter) is injected slowly intravenously until the corneal reflex just disappears. A tracheal catheter is then inserted for providing positive pressure ventilation with oxygen when the thorax is opened. With aseptic precautions the thorax and the pericardial sac are opened from the left side. With as little trauma as possible a linen suture is placed around the circumflex branch of the left coronary artery 1.0 to 2.0 cm. distal to its origin. If occlusion is to be produced in the conscious animal on a subsequent day, one hitch is taken in the suture and the loose ends are passed out through the wound. If the occlusion is to be produced under anesthesia, the suture is tied tightly at once. The pericardium and the thorax are then closed, and the animal is allowed to recover from the anesthesia if it survives.

The drugs the effects of which were studied were administered in several ways:

1. To some anesthetized dogs the xanthines were given intramuscularly before and/or after occlusion of the artery. For details, see Table II.

2. To some anesthetized dogs the xanthines were given orally for three to fifteen days before operation. Some of these animals also received the drugs intramuscularly immediately after occlusion.

3. To some anesthetized animals, atropine sulfate was given in doses of 0.2 mg. per kilogram intramuscularly immediately after occlusion of the artery.

4. To some conscious dogs a xanthine-atropine mixture was given intravenously five minutes after the occlusion. In other experiments, only atropine was given.

The results of these experiments are collected in Tables I and II.

It is apparent from an inspection of the data that the three drugs which are capable of influencing coronary blood flow, namely, theobromine sodium acetate, theophylline ethylenediamine, and atropine sulfate, modified the mortality rate after experimental coronary occlusion. The most pronounced effect was observed when theobromine sodium acetate was used. If the animal was "saturated" with the drug as a result of oral administration for several days before the occlusion, and intramuscular injection immediately thereafter, there was no mortality (five dogs). When none of this drug was given after the occlusion, two of four died. When the drug was given only immediately before and after the artery was ligated, three of twelve dogs died. The aggregate mortality rate for all dogs which received theobromine sodium acetate was 23 per cent.

The effectiveness of theophylline ethylenediamine was less when it was given in a similar manner. The aggregate mortality for all the



animals that received this drug was 56 per cent. There is a curious similarity between these figures and the data published by LeRoy and Speer.<sup>13</sup> Using a method which measured the coronary sinus outflow, they found that 60 mg. of theobromine sodium acetate, given intravenously, augmented the coronary outflow by an average amount of 150 per cent. Similar quantities of theophylline ethylenediamine increased the flow by 60 per cent. Thus it is apparent that, for the dog, as shown by two types of experiments, theobromine sodium acetate is about twice as effective as theophylline ethylenediamine.

TABLE I  
COLLECTED DATA

| TYPE OF EXPERIMENT                         | NO. OF DOGS | SUDDEN DEATH IN 24 HOURS | MORTALITY RATE (%) |
|--|-------------|--------------------------|--------------------|
| <i>A. Anesthetized Dogs</i>                |             |                          |                    |
| Controls                                   | 13          | 9                        | 70                 |
| Xanthine treated                           | 39          | 15                       | 38                 |
| Theobromine treated                        | 21          | 5                        | 23                 |
| Theophylline treated                       | 18          | 10                       | 56                 |
| Atropine treated                           | 8           | 3                        | 34                 |
| <i>B. Conscious Dogs</i>                   |             |                          |                    |
| Control                                    | 13          | 9                        | 70                 |
| Atropine treated                           | 4           | 2                        | 50                 |
| Treated with theophylline-atropine mixture | 6           | 2                        | 33                 |

TABLE II  
DETAILS OF THE ADMINISTRATION OF THE XANTHINES

| TYPE OF EXPERIMENT                           | DOSE                      | NO. OF DOGS | SUDDEN DEATHS IN 24 HOURS |
|--|---------------------------|-------------|---------------------------|
| <i>A. Theobromine Sodium Acetate Group</i>   |                           |             |                           |
| After occlusion                              | 120 mg. I.M.              | 4           | 1                         |
| Before and after occlusion                   | 120 mg. I.M. each time    | 8           | 2                         |
| Several days before                          | 450 mg. orally daily      | 4           | 2                         |
| Several days before and after                | 450 mg. orally            | 5           | 0                         |
|  | 120 mg. I.M.              |             |                           |
| Totals                                       |                           | 21          | 5 (23%)                   |
| <i>B. Theophylline Ethylenediamine Group</i> |                           |             |                           |
| After occlusion                              | 120-360 mg. I.M.          | 3           | 2                         |
| Before and after occlusion                   | 120-240 mg. I.M. each     | 2           | 1                         |
| Several days before                          | 200-300 mg. orally, daily | 2           | 1                         |
| Several days before and after                | 200-300 mg. orally        | 11          | 6                         |
|  | 120-240 mg. I.M.          |             |                           |
| Totals                                       |                           | 18          | 10 (56%)                  |
| All xanthine treated dogs                    |                           | 39          | 15 (38%)                  |

I.M., Intramuscularly.

We thought it very desirable to study the effect of atropine sulfate on the mortality rate after experimental coronary occlusion. This drug, through its ability to paralyze vagus nerve branches that transmit tonic or reflex vasoconstrictor impulses to the coronary arteries, is a definite

coronary vasodilator.<sup>14</sup> The increase in coronary flow after the administration of atropine is less than 50 per cent, but the duration of its action is much longer than that of a single intravenous dose of one of the xanthines. In anesthetized dogs, it was found that, when atropine was given intramuscularly five minutes after occlusion, the mortality rate was 34 per cent. It is probable that this effect would have been more striking had the drug been given earlier. In conscious dogs which were given atropine sulfate (0.1 mg. per kilogram) five minutes after occlusion the mortality rate was 50 per cent. There is no apparent explanation for this difference, but it was noted that dogs which were receiving atropine alone appeared to experience much more pain than when atropine and a xanthine were given. Another group of conscious dogs were given a mixture of 120 mg. of theophylline ethylenediamine and 0.1 mg. per kilogram of atropine sulfate intravenously five minutes after arterial occlusion. This was done to simulate clinical practice, where the xanthine available for intravenous use is theophylline ethylenediamine. The effectiveness of this mixture was apparent, for the mortality rate in dogs so treated was 33 per cent, whereas, in untreated ones, the rate was 70 per cent.

We have shown, therefore, that either of two means of preserving an adequate blood flow to the uninfarcted myocardium will reduce the mortality rate after a standard type of myocardial infarction caused by occlusion of a coronary artery. The mortality rate after these procedures closely parallels that reported by McEachern, Manning, and Hall<sup>11</sup> after bilateral eardiosensory denervation. In their conscious dogs, denervation reduced the mortality rate from 75 per cent to 25 per cent after a similar type of coronary artery occlusion. They assumed that this improvement was brought about by preventing reflex vagal vasoconstriction in the uninfarcted myocardium. They believe, as we do, that ischemia of the uninfarcted myocardium initiates the ventricular fibrillation which causes the sudden death of animals with myocardial infarcts. We have shown that atropine exerts a similar protective effect, presumably by inhibiting the effector (vagal) portion of the reflex. Similarly, the xanthines, which have no influence on any of the nervous elements of the reflex, but actively dilate coronary arteries by direct action, have also a protective effect. The more potent vasodilator (theobromine sodium acetate) has a more pronounced effect than the less potent one. Furthermore, in conscious animals the combination of atropine and theophylline reduced the mortality rate to a greater extent (33 per cent) than did either component of the mixture alone (atropine, 50 per cent; theophylline, 56 per cent). This last observation was particularly gratifying because it is our current practice to use a comparable mixture for the treatment of patients with acute myocardial infarction. These experiments seem to us to demonstrate clearly that the production of vasodilatation, or the inhibition of vasoconstriction, in the

uninfarcted portions of the myocardium after coronary occlusion tends to prevent the development of fatal ventricular fibrillation. They also demonstrate that this beneficial effect may be achieved by drugs of the xanthine series alone, or by atropine sulfate alone, or by a combination of the two. There appears to be little difference between the efficacy of the two types of drugs, whose only common feature is their ability to augment the coronary blood flow. Finally, it should be evident from this work that the sooner coronary vasodilatation is achieved, or vasoconstriction prevented, the more beneficial will it be. This is especially true because the primary idea in this type of therapy is to overcome or prevent the reflex vasoconstriction in the uninfarcted myocardium. It is the reflex vasoconstriction that causes the myocardial ischemia and the ventricular fibrillation which is the chief cause of early, "sudden" death in cases of coronary occlusion.

#### SUMMARY AND CONCLUSIONS

1. The mortality rate in dogs after occlusion of the circumflex branch of the left coronary artery is about 70 per cent. This rate was the same in our experiments for conscious dogs and dogs which were lightly anesthetized with morphine and nembutal.

2. The administration of theobromine sodium acetate to a dog before and/or after experimental coronary occlusion reduces the mortality rate to 23 per cent.

3. The administration of the less potent theophylline ethylenediamine, under similar circumstances, reduces the mortality rate to 56 per cent.

4. The administration of atropine sulfate reduces the mortality rate in anesthetized dogs to 34 per cent, and, in conscious dogs, to 50 per cent, after coronary occlusion.

5. The administration of a mixture of theophylline ethylenediamine and atropine sulfate to conscious dogs five minutes after arterial occlusion reduces the mortality rate from 70 per cent to 33 per cent.

6. The mortality rate after experimental occlusion of the circumflex branch of the left coronary artery in dogs may be considerably reduced by drugs which are capable of causing coronary vasodilatation, or preventing coronary vasoconstriction. Such drugs are the xanthines and atropine sulfate.

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# A CRITIQUE OF THE PLETHYSMOGRAPHIC METHOD OF MEASURING BLOOD FLOW IN THE EXTREMITIES OF MAN

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TWO types of methods are available for the quantitative measurement of blood flow in the extremities of man. The first depends upon the measurement of the thermal exchange of the extremity, and the second, on the change in the volume of the limb after obstruction of the venous outflow.

*The Calorimetric Method.*—The enclosed calorimetric method<sup>1</sup> presents certain disadvantages: (a) The assumption that the venous blood is at skin temperature after equilibration is not valid<sup>2, 3</sup>; (b) the insulation is not complete and a variable gain or loss of heat may occur<sup>4</sup>; (c) conduction and radiation cannot be evaluated<sup>5</sup>; and (d) a rapid succession of events cannot be studied.<sup>5</sup>

Surface calorimetry, when utilized under carefully controlled conditions, and when other thermal factors are considered,<sup>5-13</sup> is an important indirect method. The interpretation of thermometric studies of *deep* structures in terms of blood flow<sup>14</sup> is difficult because the origin and dissipation of the heat of these regions may depend partly on other factors. Local metabolism<sup>15</sup> and conduction<sup>5</sup> may play a significant role. Large changes in blood flow may be represented by small changes in deep temperature, for tissue temperatures are close to blood temperature.

The plethysmographic principle, although it has its limitations and disadvantages, seems more suitable as a convenient method of measuring limb blood flow.

*The Plethysmographic Method.*—Not until recently have criteria been presented for more precise studies of plethysmography, and some of the errors have been corrected.<sup>16-18</sup> An excellent analysis has been made by Wright and Phelps.<sup>18</sup> Realizing the need for a critical evaluation of plethysmography, we have independently endeavored to make a fundamental analysis of the method in order (a) to afford a critique for all general blood flow studies, especially those employing the principles of plethysmography, and (b) to ascertain the limits of technical accuracy which can be attained by a properly constructed and properly employed plethysmograph.

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The method which we employed is that of Brodie and Russell,<sup>19</sup> as used by Hewlett and van Zwaluwenburg,<sup>20</sup> for application to the extremities, with its subsequent modifications. In principle, the method determines the amount of blood flowing into an extremity by measuring the rate of volume increase of the limb in the plethysmograph when blood is prevented from leaving the part.

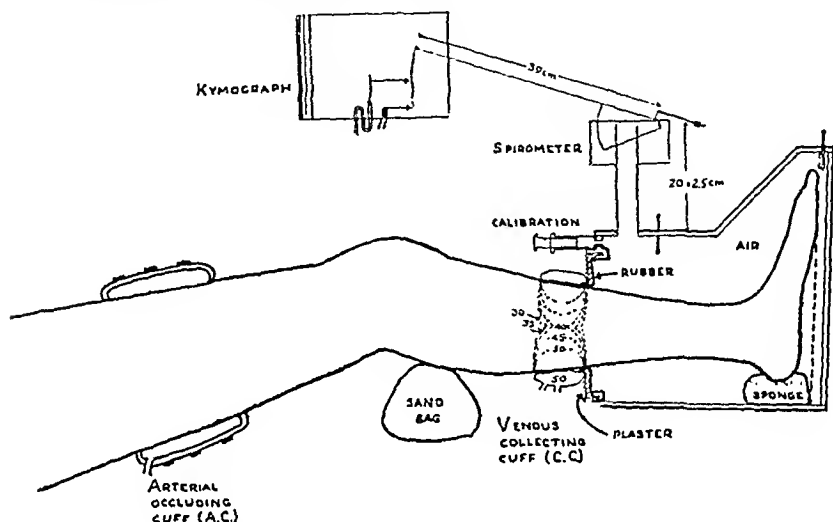


Fig. 1.—Diagram of plethysmograph used to measure blood flow in foot-leg (not to scale). It also indicates the order of magnitude of distribution of pressure in the limb, in mm. Hg. beneath the occluding cuff when the pressure in the latter is 50 mm. Hg. Discussed in text.

In practice, the limb is placed in a plethysmograph which is arranged to record changes in volume (Fig. 1). A pneumatic cuff [collecting cuff (C.C.)] is placed around the limb proximal to the plethysmograph; when this is abruptly inflated to a pressure sufficient to occlude venous outflow but not to impede arterial inflow, an increase in limb volume occurs. The rate of this volume increase indicates the rate of blood inflow. After a few seconds the rate of this volume increase declines. This results from the limited distensibility of the vascular and other tissue structures, and comes about in two ways: (a) Capillary and venous pressures rise and finally exceed the pressure imposed by the collecting cuff, with a resultant escape of blood through the veins; (b) a slowing of blood inflow occurs because of the increasing resistance in the distended limb.\* Secondary changes in the extremity may further modify the volume changes. Such changes may include alterations in vascular tone, alterations in fluid balance between the vessels and extravascular

\*The recent studies of Linton, et al.,<sup>21</sup> who used the thermostromuhr to measure arterial inflow in the intact dog hindlimb, indicate that an immediate increase in arterial inflow follows venous obstruction. These observations would invalidate the fundamental premise upon which the plethysmographic method is based. It is difficult for us to accept this evidence, however, for it purports to demonstrate that a local increase in flow follows the production of a decrease in pressure gradient over the segment studied, in the absence of changes elsewhere. It is also difficult to comprehend how, with the femoral, external iliac, and common iliac veins ligated, blood could continue to enter the iliac artery at a rate of 210 to 215 c.c. per minute over the last minute and a half of maintained occlusion with apparently no place to go.

spaces which may develop during the period of occlusion, and secondary changes in systemic blood pressure and flow.

The essential assumption which is made is that the rate of volume increase during the first few seconds *after* venous occlusion is equal to the unimpeded rate of blood flow obtaining *just prior* to the venous occlusion. In order that this assumption be valid, the collecting cuff must prevent all venous outflow long enough to permit measurement of blood flow without at the same time significantly impeding the inflow of blood.

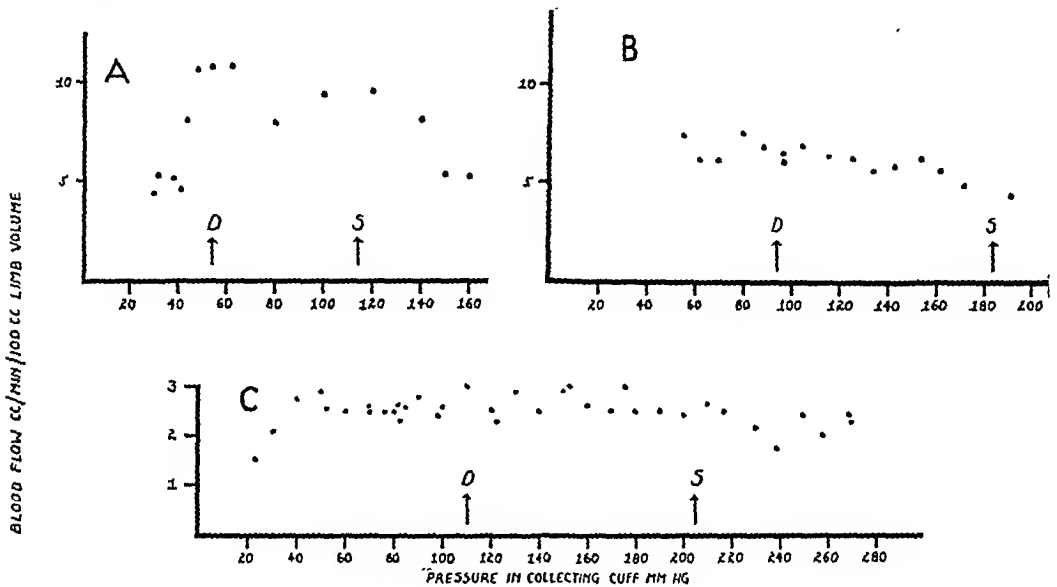


Fig. 2.—Effect of varying the pressure in the collecting cuff (see Fig. 1) on the recorded blood flow in normal subjects (A and B) and in a subject with hypertension and Raynaud's syndrome, after sympathectomy (C). D and S, in each instance, indicate diastolic and systolic blood pressure levels. Discussed in text.

1. In order to prevent venous outflow, several factors must be considered:

(a) *The inflation of the collecting cuff must be prompt.*—This is practiced universally.

(b) *The pressure in the collecting cuff must occlude all of the veins.*—It has been assumed that a pressure in the collecting cuff somewhat below diastolic pressure is effective. This was based upon the observation that the apparent blood flow increases with increasing cuff pressures to a "constant" value at cuff pressures of 50 to 100 mm. Hg.<sup>17, 20</sup> Our studies with a wider range of cuff pressures generally corroborate this; a maximal plateau extending from 50 to 120 mm. or more is observed (Fig. 2A and B). As expected, in hypertension this plateau was found to extend to a higher level. The results, however, are sufficiently variable to permit the alternative explanation that the degree of venous occlusion is incomplete, and, although it is increased by the higher cuff pressures, its effect is neutralized by a parallel decrease in arterial inflow. Although the externally applied pressure which is necessary to obstruct a brachial artery is only slightly above the

pressure within this vessel,<sup>22</sup> and veins are more collapsible than arteries, no direct evidence has been presented that complete venous occlusion is actually accomplished by the collecting cuff inflation. This factor is to be considered, especially when two long bones partially shield large vessels, as is the case in the forearm and calf. Lewis<sup>23</sup> found, however, that the venous pressure rise after cuff inflation was prompt, and, as was also noted by Levy and Brams,<sup>24</sup> reached the pressure level in the cuff, indicating that the deeper veins were distended. Evidence of a different sort, pointing to the same conclusion, has been obtained by us. A 9 cm. cuff was placed about the calves of several living subjects and one cadaver, and tissue pressures were measured within the calf beneath the cuff. A long needle was inserted for this purpose at the cuff margin or through an eyelet in the center of the cuff, and the pressures were measured directly at various directions and distances.<sup>25</sup> The distribution of pressure under such an inflated collecting cuff is outlined in Fig. 1; there is a slight pressure gradient toward the center beneath the cuff, and a steeper one toward the sides. This evidence suggests that, at 50 mm. Hg of cuff pressure, the pressure distribution in the tissue beneath the cuff would be sufficient to occlude all collapsible veins. No evidence is adduced from this study as to the effect upon blood pathways in bone, or as to the minimum effective width of the cuff. A test of the adequacy of cuff width was undertaken by comparing the apparent blood flow in a normal subject with a 9 cm. and a 5 cm. cuff of the type described by Abramson, et al.<sup>17</sup> The flow with the wide cuff was 3.2 to 4.1, and, with the narrow cuff, 3.9 to 4.2 c.c./min./100 c.c. of limb volume.

(c) *The pressure in the collecting cuff must not decrease arterial inflow.*—Our experiments on the effect of increasing cuff pressure on apparent blood flow in normal subjects (Fig. 2) and in patients with hypertensive vascular disease showed that the blood flow measurement was sometimes the same until cuff pressures well above the systolic blood pressure were reached. Above this point the blood flow measurements decreased, indicating obstruction of arterial inflow. It would therefore appear that arterial inflow at the moment of inflation of the cuff is not altered with the cuff pressures ordinarily employed.

2. Even if the venous occlusion is complete, there must be a *sufficient period of time to make a blood flow measurement* before the rate of blood accumulation is significantly altered. From purely physical considerations, as soon as an impediment is placed in the path of flowing fluid, a readjustment of the pressure in the entire fluid system occurs. The validity of the assumption that this does not significantly alter the rate of blood flow during the first few seconds after the application of venous occlusion would require that the change in distribution of pressure be small. No such evidence has been presented. In practice, the interval immediately after cuff inflation is usually not utilized because



of the presence of artifacts at this time. It is the custom to use the average rate of volume increase during the three or four seconds after the initial artifact.

The volume curve of the leg after venous occlusion appears as a curve in relation to time. If the equation for this curve were known, its first differential would indicate the rate of change in volume with time, and the value of the first differential at the instant of occlusion ( $t \equiv 0$ , i.e., the tangent to the volume curve at this point) would measure the rate of blood flow at the moment of venous occlusion. A practical application of this can be obtained by direct extrapolation of the graph derived by drawing tangents to the volume curve at several points and plotting their values against time. Linear or logarithmic plots of these values may yield a straight line (depending upon the order of the equation of the volume curve) which may be extrapolated to zero time. Should the rate of blood flow at zero time be found to vary significantly from the average rate as usually derived, the latter could not be taken to indicate the rate of flow accurately.

This was actually tested on figures published by Burton,<sup>26</sup> which were derived with an adequate recording system. Extrapolated curves were made of various plottings of the first differential, derived graphically by constructing tangents at various points in time. It was found that the extrapolated rates of blood flow so derived were from 20 to 40 per cent greater than the average estimated rates in these cases. Since the zero rate of blood flow is the more constant, and the factors determining the distensibility of the limb are the more variable, it would appear desirable to obtain the extrapolated blood flow, particularly when the method used is the limiting factor in the accuracy of the study.

*A Consideration of the Placement of the Collecting Cuff and Its Inflation.*—Inflation of the collecting cuff causes compression and distortion of the limb in its immediate neighborhood. The artifact introduced by the local limb distortion has led many workers to recommend placing the collecting cuff at a definite distance proximal to the recording plethysmograph.<sup>17, 20</sup> Others have, instead, separated the collecting cuff and plethysmograph by an intervening joint,<sup>16, 18, 27</sup> as a matter of convenience, or by an unstated distance. Since the volume increase occurs in all parts distal to the collecting cuff, the change in volume recorded by the plethysmograph when the cuff is at a distance from it represents only a portion of the inflow, and not necessarily a constant portion (Fig. 3). Although this has been noted,<sup>18</sup> and workers in dealing with forearm flow have realized the error of assuming that the segment distal to the plethysmograph increased in volume by an amount equal to its arterial supply,<sup>16, 27</sup> insufficient attention has been directed to this obvious source of error.

A series of experiments was undertaken to evaluate the significance of this factor, as well as to throw some light on the nature of the initial artifact which appears when the collecting cuff is inflated.

As a first step, a wide, leather-backed cuff was placed on the mid-thigh for the purpose of occluding the arterial inflow. When this cuff was abruptly inflated to a pressure of 250 to 350 mm. Hg., a slow increase in the recorded plethysmographie volume appeared (Fig. 4d

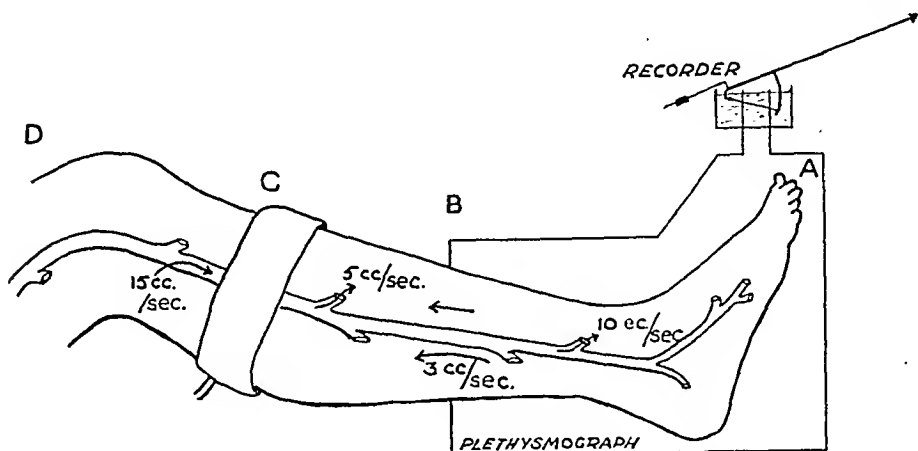


Fig. 3.—Diagram to show the possibly unequal distribution of flow in the limb distal to an occluding cuff, between the portions of the limb within and without the plethysmograph. In this diagram the arterial supply to the limb *ABCD* is assumed to be such that 15 c.c./sec. pass into segment *CBA* below the pneumatic cuff, placed at *C*. Of this, it is assumed that  $\frac{1}{3}$  is distributed to segment *CB*, and  $\frac{2}{3}$  to segment *BA*, enclosed in a recording plethysmograph. When cuff *C* is inflated, obstructing the venous return, the segment *CBA* will increase in volume. Only the volume increase of segment *BA* will be recorded by the plethysmograph, which should indicate an initial rise of 10 c.c./sec. However, there is nothing to prevent some redistribution of the 15 c.c./sec. entering *CBA*, between *CB* and *BA*. For example, if 3 c.c. are transferred to *CB* in the first second, the plethysmograph would erroneously indicate a flow of 7 c.c./sec. A similar error would occur if the plethysmograph were arranged so that *CB* were in it, and *BA* outside of it. In short, redistribution of flow necessitates the measurement of the volume changes of all tissues receiving blood distal to *C*.

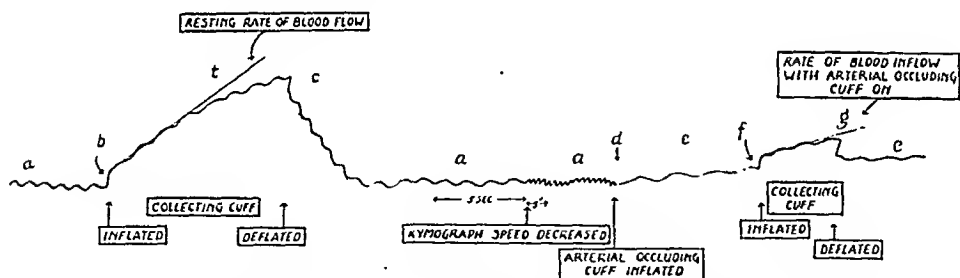


Fig. 4.—A record of limb volume, showing pulse and respiratory variations (*a*), the artifact (*b*) and volume increase obtained when collecting cuff (see Fig. 1) is inflated, with tangent (*t*) representing determination of blood flow, the artifact and volume decrease (*c*) on release of pressure in collecting cuff; abolition of pulsatile variations (*e*) when a cuff on the thigh (see Fig. 1) is inflated at (*d*) to a pressure of 250 to 300 mm. Hg. for the purpose of occluding arterial inflow, and, finally, the collecting cuff artifact (*f*) after subsequent inflation of collecting cuff, and the tangent (*g*) giving the rate of "blood flow" which occurs even when the arterial occluding cuff is inflated. Discussed in text.

and *e*). The increase in volume subsequent to arterial occlusion *alone* was relatively large for thirty seconds, and then became smaller and linear over the observed six minutes. This might represent blood redistribution between the part of the limb inside and outside the plethysmograph, or, more likely, as Lewis and Grant<sup>29</sup> suggested, it might represent continuing blood entry into the leg despite the arterial occlusion. The quantity of this persisting flow to the enclosed portion of the limb

ought to be ascertainable by applying the collecting cuff *at* the plethysmograph. When the arterial occlusion was maintained, inflation of the collecting cuff to 50 mm. Hg produced the same initial artifact (Fig. 4f) as when no arterial occlusion was present (b). This was followed by a continuous increase in recorded volume (e) which was greater than before the collecting cuff inflation (g). The initial artifact was the result, in part at least, of distortion of the limb by the collecting cuff inflation, which displaced volume within the plethysmograph. Experiments showed (Fig. 5) that this artifact varies in an approximately linear fashion with the applied collecting cuff pressure. The magnitude at any pressure showed individual variations in different experiments, e.g., it varied from 2 to 5 e.c. at 75 mm. Hg.

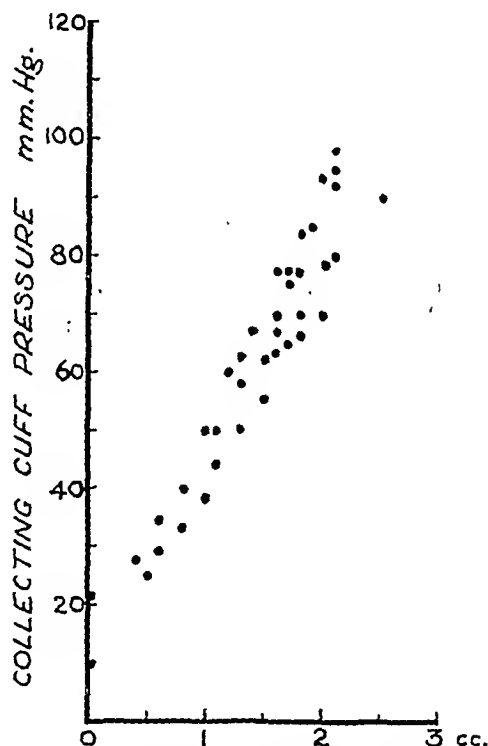


Fig. 5.—Magnitude of initial displacement artifact after inflation to various levels of the collecting cuff when it is placed at plethysmograph (see Fig. 1), carried out after the artery was occluded at mid-thigh by the arterial occluding cuff (see Fig. 1).

This initial artifact decreased when the collecting cuff was applied at a distance from the plethysmograph; in one experiment the relation was  $6\frac{1}{2}:3:1\frac{1}{2}$  at distances of 0, 4, and 8 cm., respectively, but, in another, the artifact was the same at a distance of 8 cm. from the plethysmograph as at 0 cm. distance, and both were greater than at a distance of 4 cm.

The continuous increase in volume after the initial artifact, which was observed when the collecting cuff was inflated with the arterial inflow occluded by a mid-thigh cuff (Fig. 4g), may have been due to (a) a secondary, slow component of the initial artifact caused by delay in the

readjustment of the tissues after the application of the collecting cuff, or (b) to flow via bone or other unoccluded arteries.<sup>23</sup>

The rate of this continuous increase in volume decreased progressively more than it did over the same period when the venous cuff was not inflated. This suggested that filling of the limb acted as an impediment to further flow, and so favored the view that this secondary volume change is due, in part at least, to flow via bone or other unoccluded arteries. After the first sixty to seventy seconds of this secondary volume change, this appeared to be the only factor involved. Thus, in the three sets of experiments in which an analysis was made, no definite variation in the rate of volume change occurred with the pressure level existing in the collecting cuff; the rate was approximately the same in all three. This was true also in the four sets of experiments in which the cuff-plethysmograph distance was varied. The amount of volume change was not the same in all subjects or at all levels of occluding pressure, but varied from 0.0 c.c. to 1.0 c.c./min./100 c.c. of limb volume.

The changes in the first part (the first sixty to seventy seconds) of the secondary volume increase suggested that an artifact was involved in causing the limb volume to vary at this time. Thus, the volume change in the first seventy seconds was found to vary with the pressure level in the collecting cuff, and the volume change appeared to vary in a "cyclic" fashion with the distance of the collecting cuff from the plethysmograph.

These results suggest that, after the application of the collecting cuff, an initial, large artifact occurs which varies with the applied pressure and the distance between cuff and plethysmograph. The amount is a function of the applied pressure, but cannot be accurately related to cuff-plethysmograph distance. It is attributed primarily to the displacement of the tissues by cuff application. The primary artifact is followed by a secondary artifact, lasting sixty to seventy seconds, which may be due to continuation of the tissue displacement or to overdamping of the recorder. (The latter can be eliminated by approximating critical damping in the recorder.) In addition, the results show that it is *not* possible to eliminate all the arterial inflow by use of a mid-thigh arterial cuff, even when the pressure is elevated well above the systolic pressure. This is because vessels within bones and perhaps in other localities cannot be occluded. This latter fact does not interfere with simple measurements of blood flow in plethysmographic studies, but the primary and secondary artifacts are of prime importance. Since it is not easy, according to our experience, to eliminate these artifacts by removing the collecting cuff from the plethysmograph, it was deemed desirable to keep the collecting cuff at the plethysmograph, where the magnitude of the primary and secondary artifacts is more predictable, and this practice is recommended, especially because no consideration need then be given to the flow partition between that part of the limb below the collecting cuff inside the plethysmograph and that outside it.

*The Plethysmograph and Volume Recorder.*—The plethysmograph should be light in weight, rigid, chemically inert, and insulated or jacketed. Its shape and size should, as a rule, be such as to keep the volume of the plethysmograph as small as possible, and yet large enough to accommodate the largest limb to be studied.

Ideally, a gas-containing plethysmograph which can be maintained under controlled conditions of temperature, humidity, and initial volume would least disturb normal conditions; air is the gas generally employed. An air-containing plethysmograph would require a true volume recorder, and no ideal recorder, independent of pressure changes, has yet been developed. The air-filled system would decrease the sensitivity of recorders now available, and increase the time lag in the recording. There are no published studies bearing on the effects of local humidity changes in such air-filled plethysmographs, particularly thermal effects caused by the evaporation or condensation of moisture. These effects could be minimized by having the air saturated with moisture. A more practical objection to air-containing instruments is the large temperature coefficient of expansion of gas; as a result, significant volume changes in the plethysmograph can be caused by slight temperature changes. Thus, a change of  $0.1^{\circ}$  C. at  $27^{\circ}$  C. and at atmospheric pressure would increase the volume of each liter in the plethysmograph by 0.33 c.c. Since in limb plethysmographs the air space is several liters, the magnitude of gas expansion and contraction caused by slight differences in temperature may produce a significant error. Moreover, the measurement of blood flow requires stoppage of the venous outflow, and this accumulation of blood in the limb will tend to dissipate more heat from the limb to the surrounding air at a time when constancy of temperature is most essential. Similar changes will occur when the rate of blood flow is altered and when the environmental temperature is altered—both common occurrences.

Fluid, in certain respects, is more convenient to use in the plethysmograph than air. It is virtually incompressible and thus gives rapid transmission of volume changes; it has a small coefficient of thermal expansion, and, in the case of water, a small coefficient of heat conduction. It is also easier to detect leakage of fluid than of gas. However, the use of fluid places the limb in an abnormal environment which prevents evaporation and physically may alter the response of the skin vessels. It also has the disadvantage of imposing hydrostatic pressure upon the limb, the approximate mean value of which is half the depth of immersion, although the effective mean value may be higher if the greater part of the vascular bed is more deeply immersed; these factors may alter blood flow relationships.<sup>30</sup> Another disadvantage of a fluid-filled plethysmograph is the restriction imposed on the position of the limb. It is usually desirable to have the entrance of the part into the plethysmograph at a region which is subjected to little hydrostatic pressure, so that an adequate seal may be effected without producing

constriction of the limb. Finally, in utilizing a fluid-filled plethysmograph—completely or almost completely filled—a large pressure change may accompany the volume changes unless care is taken (a) to adjust the fluid level so that no increase in its height occurs, and (b) to employ a so-called volume type of recorder, i.e., one with large available space moving under little pressure differential. The disadvantages of an appreciable pressure change are that (a) it causes leaks around the entrance seal because this should not be too tight, and (b) it causes an increase in pressure upon the limb, thereby opposing the arterial inflow.<sup>30</sup>

It is apparent from this discussion that the errors and limits of each individual plethysmograph should be ascertained in order to estimate its accuracy and constancy of performance.

Not only the plethysmograph, but the volume recorder, is important with respect to accuracy and constancy of observation. Most of the earlier workers used a modification of the Brodie bellows because of its relative sensitivity and small mass. The particular inaccuracy introduced by such a bellows is that, even if it is prefolded so that it will fold and unfold in a predictable fashion, which is usually not the case with a small bellows, the distortability of the Cargile membrane or goat skin will not permit constancy of calibration. The Brodie bellows, like all types of so-called volume recorders, is activated by pressure changes sufficient to overcome the effective resistance to motion or change of motion, i.e., its inertia. Another disadvantage of the Brodie bellows is that gravity operates to aid motion in one direction and hinders it in the opposite direction. Counterbalanced spirometers<sup>31</sup> avoid this last disadvantage, although they are usually counterbalanced in only one position.

The usual types of recording instruments are so constructed that they are suitable only for relatively slow frequencies; they cannot accurately portray the pulsatory variations during the heart cycle, and each should be tested to ascertain its suitability for measurements of mean flow. For pulsatory flow, a recorder which has a higher natural vibration frequency and is ideally damped is required. The frictional resistance of the writing point and the effective mass of the writing lever must be included in evaluating the characteristics of any volume recorder. Optical recording would eliminate this. Electrical or radio amplifying recorders also require examination from the foregoing standpoint to establish their accuracy.

A further source of error arises from the arcing of the writing lever on the recording paper, for the writing levers of most volume recorders operate from a fulcrum. Thus the ordinates (volume change) are not vertical, but curvilinear, whereas the abscissae (time) are horizontal. The curvilinear ordinates introduce parallax (Fig. 6), and also do not permit accurate construction of tangents which can only be drawn in a Cartesian system of rectilinear coordinates. Hence, the curvilinear

character of the ordinates must not be overlooked, and the graph cannot be considered as rectilinear in construction.

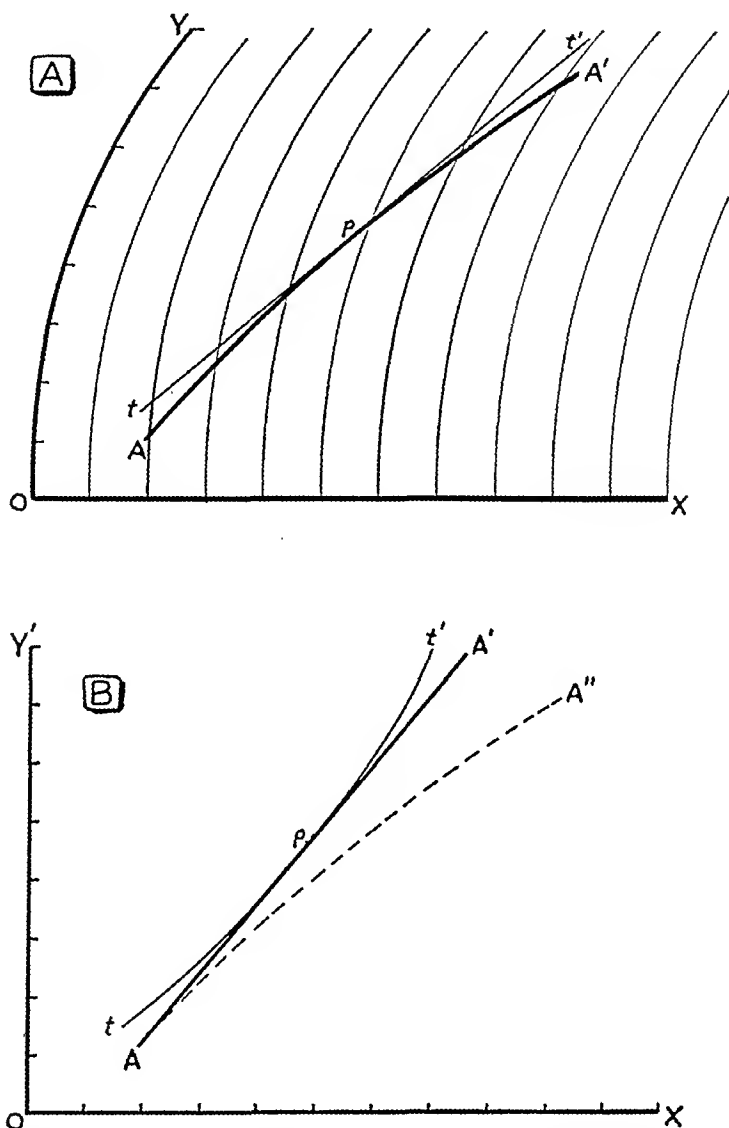


Fig. 6.—Diagram to show the error of the tangent in curvilinear coordinates. In A,  $OX$  and  $OY$  are the coordinates of limb volume records, such as were used in these studies.  $OX$  = time and is rectilinear;  $OY$  = volume and is curvilinear.  $AA'$  represents the equation of a straight line, which, when plotted on these coordinates, becomes a curve. The true tangent to  $AA'$  is  $AA'$  itself. If a "tangent line"  $tpt'$  is applied to curve  $AA'$  at  $p$ , this is in reality a curve, and therefore is not a true tangent. In B, representing rectilinear coordinates,  $OY'$  and  $OX$  have otherwise the same meaning as in drawing A; the line  $AA'$  is correctly plotted as a straight line; and  $tpt'$ , its supposed "tangent," when plotted correctly here, is a curve.  $AA''$  represents the erroneous curve representing the line  $AA'$ , which is produced in a curvilinear system, if the curvilinear system is assumed to be rectilinear (i.e., if parallax is neglected). Discussed in text.

Several other considerations have been given considerable attention by other workers. An important factor, of course, is the relation of the instrument to the level of the heart.<sup>20, 29</sup> Another is the possible limitation of the method for limbs with an impaired circulation, a collateral circulation, or both.<sup>30</sup> By convention, the unit for expressing flow<sup>20</sup> is volume change in c.c./min./100 c.c. of limb volume, or c.c./min. The minimal time between successive measurements was ascertained; it

was found that measurements can be made every ten seconds without influencing the results.

*The Final Assembly Used in This Study.*—After the foregoing analysis of the principles of proper plethysmographic recording was made, the following assembly was utilized because it was a practical, convenient arrangement in which errors could be obviated or known.

For the foot-leg we have adapted the large, double-walled plethysmograph of Abramson, et al.<sup>17</sup> This, as designed for use with water, required that the leg be dependent. Calibrations for volume and rate of change in volume, when the instrument contained air, as well as comparative experiments done with water and with air, revealed no significant difference, and in all subsequent studies it was used as an air-containing plethysmograph, usually with the limb within 10 cm. of the heart level, and the patient in a comfortable supine position, with the leg horizontal. Circulation of air for heating was provided by a detachable, thermostatically controlled hot-air blower. The plethysmograph volume was 6,500 c.e. A tube, 2.5 cm. in diameter and 20 cm. in length, connected the spirometer to the plethysmograph.

For the recording instrument, small spirometers of the Gad type were constructed; they were of several capacities, up to 60 c.e., and sizes, up to 3.5 by 5.8 cm., and weights (including counterbalance), up to 12 Gm. Each was made of three pieces of x-ray film, cemented together by a solution of x-ray film in acetone (one piece may be used). To this was fastened a metal-wire fulcrum, a counterbalancing arm, and an aluminum recording arm with an effective radius of 39 cm., on which was cemented a conical celluloid pen such as is used for barographic recording. The capacity of this pen was increased and adapted for vertical writing by cementing upon it a small, truncated, celluloid or cellophane cylinder. The recorder pivoted on notches in the edge of a container 8 by 5.5 by 5 cm., which contained a mixture of glycerine and water. A 2.5 cm. tube extended through the bottom, reaching above the fluid level. The proportions of glycerine and water were chosen to damp the instrument approximately critically. The damping was produced by the amount of surface of the spirometer in contact with the liquid, the nature of the liquid, friction of the pivotal bearings, friction at the writing point, the flexibility of the writing arm, and the position of the counterbalance. The surface relation of spirometer to fluid was large and could be made variable. Smaller recorders with proportionately more surface may be overdamped unless less viscous liquids are used. This could be adjusted by using varying proportions of alcohol, glycerine, and water; the specific gravity in this way could be varied from 0.8 to 1.26, and the viscosity, from 10 to 8,700  $\eta$ . In glycerine mixtures as we have used them, the water may be replaced as it evaporates, in order to keep the composition roughly the same. Freeman and Zeller<sup>31</sup> have used a similar volume recorder in mineral oil, and Kolin<sup>32</sup> has suggested glycerine to effect aperiodic damping.



In the arrangement used by us, a pressure difference of less than 0.02 mm. Hg will set the spirometer in motion.

The frequency response characteristics for volume and rate of volume change were ascertained for the recorder alone and for the plethysmograph and recorder, by attaching, in a closed system, without valves, a cylinder-piston pump driven from a circular cam, so that the volume increase and decrease that were produced were in the form of a sine wave. The percentage of error in recording volume changes was ascertained for various volumes at the various frequencies of the pump (Fig. 7A). This error is the same as that which occurs in recording the average rate of volume change at these stroke frequencies for the several magnitudes of stroke volume. In addition, recorded maximum rates of volume change were obtained by drawing the maximal tangents to these curves, and these were compared to the theoretical *maximal* rate of volume change for the various volumes and frequencies. The percentage  $\left( \frac{\text{maximum recorded rate}}{\text{maximum theoretical rate}} \times 100 \right)$  so obtained is a more significant indication of the over-all accuracy of the instrument in recording rate of change over the various ranges of volume and over the various ranges of rates of change in volume. The values indicating this accuracy were plotted according to frequency of the pump (Fig. 7B) and according to the maximum rate of change of volume (Fig. 7C). These plots include not only the error of the instrument, but also the error of calculating the results.

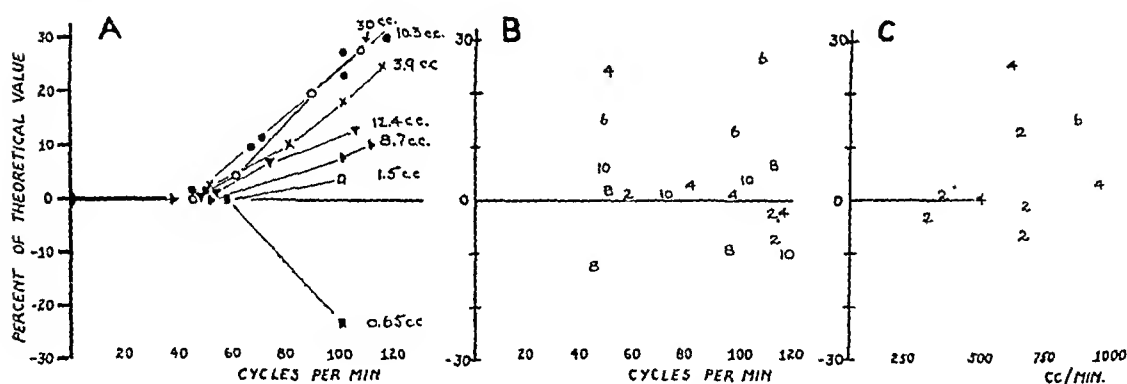


Fig. 7.—A shows the variation in accuracy of recording volume as the frequency of the pump is changed at the different stroke volumes indicated. B shows the variation in accuracy of recording (and computing) maximal rate of change in volume as the frequency of "sine wave" pump is changed. The figures indicated at points on graph represent stroke volume in cubic centimeters. If  $V$  is the stroke volume of the pump and  $f$  is the cycle length of the pump, the tangent representing the theoretical maximum rate of change in volume  $= \pi Vf$ . C shows the variation in accuracy of volume recorder in recording (and computing) maximal rate of change in volume. The values of A, calculated in c.c./min., are plotted against the theoretical maximal rate of volume change.

Such a determination of the characteristics of a volume recorder are especially important when one is attempting to measure the rate of change in volume. Thus, if +10 c.c. is recorded with an error of  $\pm 10$  per cent as +10 c.c.  $\pm 1$  c.c., and the increase occurring within 0.1 second is recorded only after 0.2 second, the rate of change in volume recorded

is 50 c.c./sec.  $\pm$  5 c.c., but the actual rate is 100 c.c./sec., and the true error of recording is not the error of the volume recording but the combined errors of volume and rate recording. In the example given this is actually 45 to 55 per cent.

After the characteristics of the instrument were known, certain precautions were essential in regard to the placement of the limb in the plethysmograph. The limb was supported by placing a sponge beneath the heel and sandbags below the knee (Fig. 1). Airtight, noneonstricting closure was obtained by means of a sheet of rubber, 1 mm. thick, in which an ovoid hole was cut to the appropriate size for the desired height on the leg. Rubber cement was applied about the leg and along the edge of the rubber sheet in a band 0.5 cm. wide, and the sheet was then everted toward the toes and attached as a cuff to the leg. After the cement had dried and the attachment of the sheet had become secure, the sheet was slightly stretched and fastened over the opening of the plethysmograph with a metal ring. Thus, a closure diaphragm was made which, by proper selection of size of opening and tension on the rubber, would not exert significant pressure upon the limb. In fact, care was taken to avoid traction on the skin. Once the diaphragm had been fitted in place and tested for leaks, a plaster of paris paste, not quite thin enough to pour, was prepared and smeared over the outside of the rubber to make a diaphragm 2 to 4 mm. in thickness. This set in two or three minutes, forming a light, rigid closure. This method is similar to that of Wright and Phelps,<sup>18</sup> who used Unna's paste instead of a rubber sheet. The modification we employed prevents leaks more effectively; the disadvantage is that it permits but slight movements of the leg.

When the apparatus was ready for use, it was again tested for leaks. This was conveniently accomplished by deliberately setting the spirometer recorder off balance, first in one direction and then in the other; leaks were shown by drifts of the recorder. When leaks were absent, the collecting cuff, 5 cm. in width, was placed about the leg close to the plaster seal. A 16 cm., leather-backed cuff had been previously strapped smoothly but loosely about the thigh for use as an arterial occluding cuff in studies on reactive hyperemia. Each cuff was connected to a pressure tank and manometer under suitable pressure, with a valve arrangement to permit abrupt inflation and deflation of the cuffs. The arterial occluding cuff was inflated from a 20 liter metal drum, and the proper pressure level in it was set with a pump. The venous occluding cuff was inflated from two such drums, and the pressure level was set in them by hand with a rubber sphygmomanometer bulb. A damped mercury manometer, carrying a float and pen writer, was connected to the collecting cuff to record the time and speed of inflation and deflation, and the duration and pressure level of inflation.

All tracings are recorded in ink upon a vertical paper, 30 cm. wide. This is driven from a continuous roll by a friction drive, operated by a

synchrous motor with six geared forward speeds.\* The paper speed is constant within 1 per cent over the range of speeds available, namely, 9.5 to 1,730 mm./minute. Time and signal markings are recorded by continuous feed pens on the signal magnets. Time impulses at  $\frac{1}{5}$  to 5 seconds intervals are delivered from a specially built A.C. timer.\* After the subject had been at rest for thirty minutes, tracings were made. Normally, pulsations were noted, and, with the kymograph running, the collecting cuff was inflated abruptly. After a curve of sufficient duration was obtained, the cuff was deflated. Each such recording occupied a few seconds and could be repeated quickly. Actual sections of a record are shown in Fig. 8.

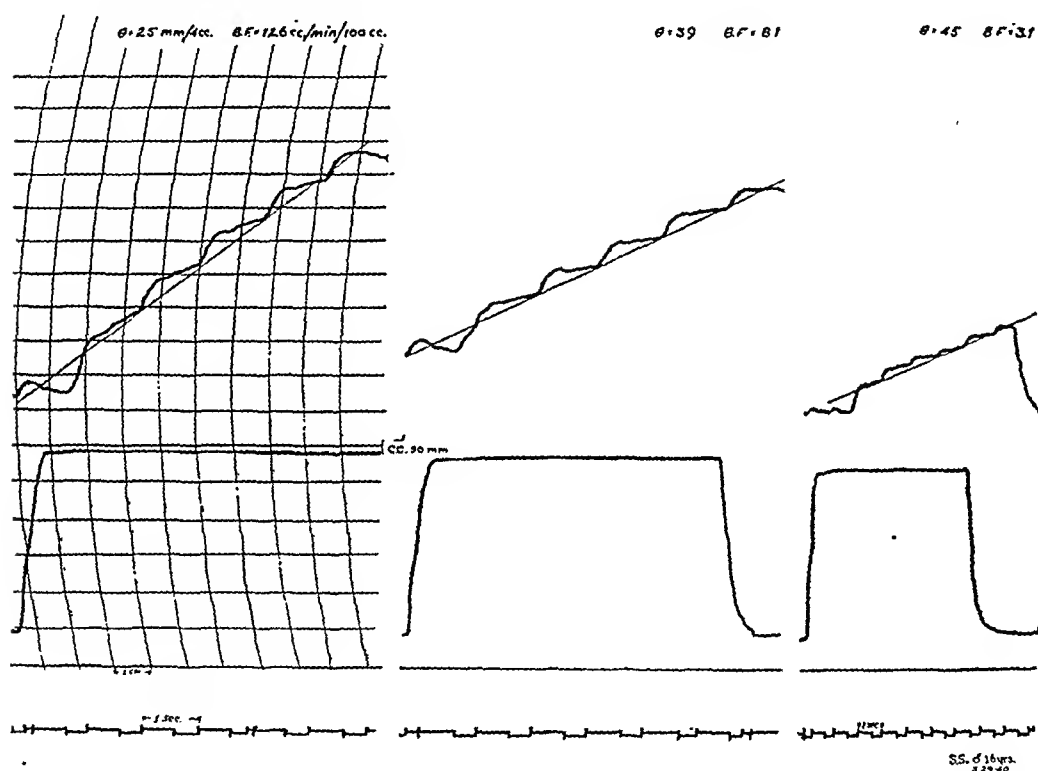


Fig. 8.—Sections of a kymographic record, showing, from above down, (1) volume record after inflation of collecting cuff and the tangent indicating rate of blood flow, (2) record of pressure within collecting cuff, (3) base line, (4) time in seconds. Three successive determinations are shown; in the first the curvilinear time lines 1 cm. apart, and the horizontal volume lines, 2 c.c. apart, are drawn in. In the upper right hand corner of each graph the tangent value and its corresponding blood flow are indicated. This figure is part of a series of curves taken during subsidence of reactive hyperemia. It illustrates the procedure of slowing the rate of the drum (3rd graph) to make the tangent approach 45° to simplify calculation of blood flow. Note the slight initial artifact on inflating the collecting cuff, and the contour of the individual pulsations, which bear a superficial resemblance to a pulse wave contour. The parallax between the volume record and the intra-cuff pressure record are deliberate, to permit full excursions of both writing points.

In each single experiment, requiring one to two and one-half hours, from ten to fifty resting flows were obtained as controls. In the experiments with reactive hyperemia, repeated arterial occlusions were produced for selected periods of time. Flows were measured at the moment of release of the occlusion, as was done by Lewis and Grant,<sup>29</sup> by inflat-

\*Designed and constructed by Mr. S. F. Gaddas.

ing the collecting cuff just before release of the arterial cuff,\* and this was followed by making measurements every ten to fifteen seconds, or less frequently, as required, until resting values were reached. In this way the curve of change in flow was ascertained. If only a single observation is made (e.g., at ten seconds after release<sup>27, 33</sup>), this may not depict the maximal flow, or even a constant proportion of it.

In the experiments with elevated bath temperatures, heating was interrupted during the actual flow measurement. Under these conditions, long-time volume changes were not considered reliable. Absence of volume changes over the period of measurement (three to five seconds) was tested by demonstrating that there was no change in the base line during an equivalent interval preceding or succeeding this period. In the instances in which no marked change in temperature occurred, relative "basal" changes in limb volume were noted before the inflation of the collecting cuff.

Movements of the limb and coughing and speaking are detectable by irregularities in the tracing. Adequacy of arterial occlusion was shown by (a) abolition of pulsations and (b) absence of blood flow on applying the collecting cuff. Room and boot temperatures were taken. At the conclusion of each experiment the leg volume was measured to within 10 c.c. by overflow displacement of water, immersing the dependent leg to the level of the rubber and plaster seal. (This gives the volume of leg partially filled with blood.)

*Manner and Accuracy of Measuring the Recorded Volume Changes, and the Rate of Change.*—The record was measured by placing it under two celluloid sheets on a drawing board. Upon one there are a horizontal base line (to which the base line of the tracing is matched) and a parallel calibration chart obtained from calibration of the empty apparatus. Upon the other celluloid sheet there are parallel, vertically oriented, curvilinear ordinates 5 mm. apart, drawn from a radius equal to that of the writing arm of the recorder. All points upon each curvilinear line, when properly oriented to the horizontal base line, therefore represent the same moment in time. The interval included between these lines depends, of course, upon the speed of the recording paper. With these two celluloid sheets superimposed, the volume change and time can be read directly, as from any rectilinear graph.

Inasmuch as a pressure differential of less than 0.02 mm. Hg sets and maintains the spirometer in motion, it can be considered essentially as a volume recorder. Since the closure of the plethysmograph when in use is essentially rigid, all volume changes are transmitted to the recorder, and therefore the calibration of the empty instrument is suitable for use. A check calibration for several points of the scale was made

\*Sometimes an artifact in volume was produced here by movement of the leg on release of the occluding cuff. This could often be minimized by placing the cuff so that it would not come against any support when inflated, or it could be avoided by measuring blood flow in the usual manner one to two seconds after the release of the occluding cuff; the more predictable artifact of the collecting cuff was present in this case.

in every case with the limb in place, usually with the artery occluded. For any error (caused by warping of the spirometer) the proportionate correction factor was inserted in the calculation.

It is incorrect to apply the theory of tangents to a curvilinear system in obtaining rate of volume change. The line tangent to our recorded curve would, in this system, be a curve, not a straight line, and it would vary with the angle from the vertical which the curvilinear line makes at the point to be measured. An attempt was made to overcome this error. We selected a fixed unit of volume change (4 c.c.) and ascertained the time (in minutes) required for this volume increase on a "tangent" drawn at the appropriate point. This was done to keep the error of curvature of the volume ordinates more nearly constant than could be done by ascertaining the volume change for a fixed time period.

Thus, rate of blood flow in cubic centimeters per minute equals  $\frac{4}{t}$

The "tangent" line was drawn to fit the initial second or two of the curve. This was taken after the artifact was inscribed (usually after 0.2 second), and, when after vibrations were present, a mean curve was selected.

The calculation was actually done as follows:

$$\text{Rate of blood flow (in c.c./min.)} = \frac{4}{t} \times R$$

where  $R = \frac{\text{actual volume calibration}}{\text{recorded volume calibration}}$ , and  $t = \text{time in minutes}$ .

Time,  $t$ , is expressed as the distance  $\theta$  (in mm.), traveled at the set speeds 1 to 6 of the kymograph.

$$t \text{ (in min.)} = \frac{\theta}{S_n}$$

where  $S_n$  represents the paper speed (in mm./min.).

Rate of blood flow (in c.c./min./100 c.c. limb volume) =

$$\frac{4 R S_n 100}{V \theta} = \left[ \frac{400 R S}{V} \right] \frac{1}{\theta}$$

where  $V = \text{volume of limb (in c.c.)}$ .

The expression  $\frac{400 R S_n}{V}$  is a constant ( $F_n$ ) for each experiment, selecting for  $S_n$  the speed  $S_{1-6}$ . It is most convenient for calculation to select a speed so that the tangent will have an angle near  $45^\circ$  (Fig. 8). With this factor ( $F_n$ ) as a slide rule setting, flow may be calculated for each tangent distance  $\theta$  in a single direct operation.

In short, blood flow =  $\frac{F_n}{\theta}$  in c.c./min./100 c.c. limb volume.

*Observations on Resting and Maximal Blood Flow in the Legs of Normal Subjects.*—With the method described, nineteen experiments were performed on seventeen normal subjects. In six patients the resting blood flow was measured with the leg dependent, and, in thirteen, with the leg horizontal. In the former the resting flow was 0.6 to 7.0 cc./

min./100 c.c. limb volume, and, in the latter, 0.5 to 6.0 c.c./min./100 c.c. limb volume. These observations are summarized in Fig. 9; the subjects in each series are arranged according to age.

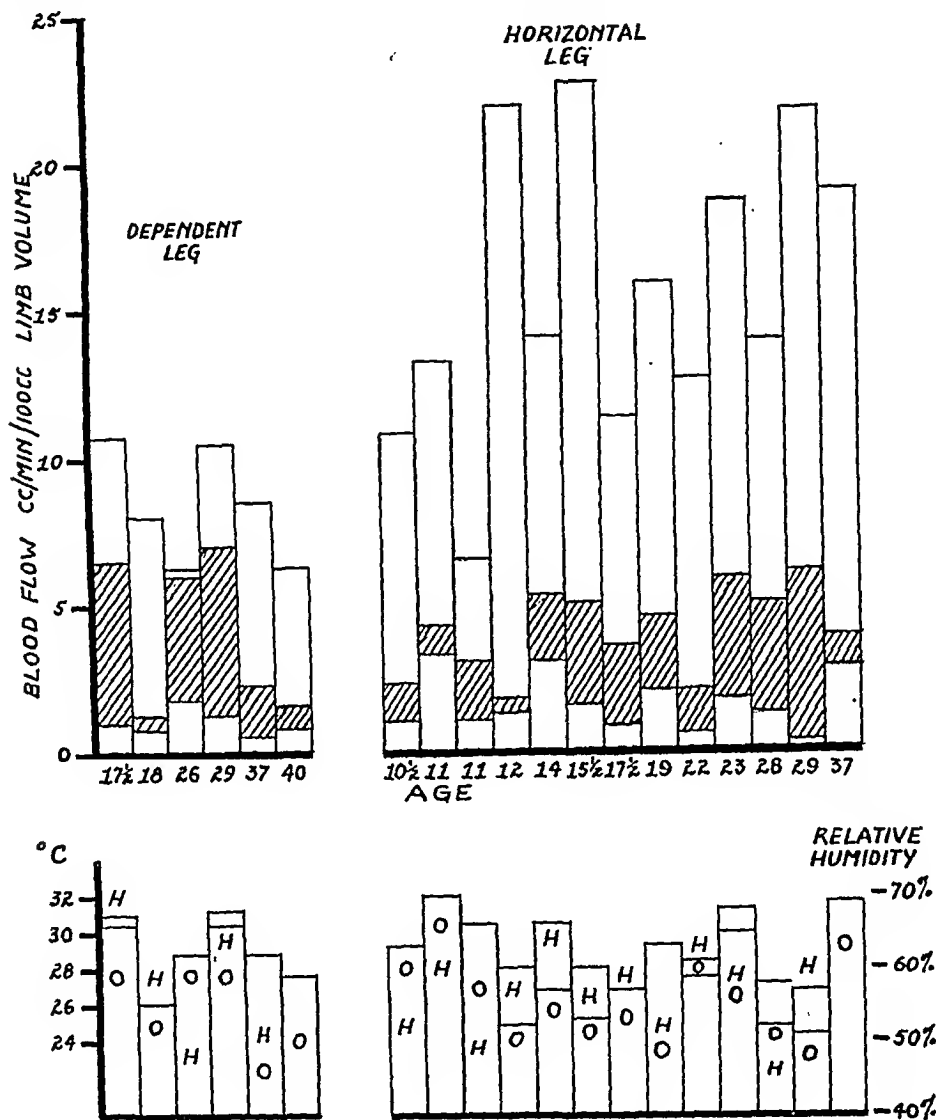


Fig. 9.—Blood flow in dependent and in horizontal position of foot-leg of normal subjects, arranged according to age. Maximum flow during reactive hyperemia shown by height of columns. Resting flow range shown by cross-hatching. Temperature in plethysmograph is shown by single or parallel horizontal lines; room temperature, by open circles; and relative humidity, by H.

In each of these experiments reactive hyperemia was induced by producing arterial occlusion for four to twelve minutes. The maximum flow on release was found to be 6.4 to 10.8 c.c./min./100 c.c. limb volume in the experiments with the leg dependent and 6.3 to 22.5 c.c./min./100 c.c. limb volume with the limb horizontal (Fig. 9). Such differences were seen when the flow with reactive hyperemia was measured on the same subject on different days with the leg horizontal and dependent. Typical examples of the time course of reactive hyperemia are shown in Fig. 10.

Comparative blood flow measurements on the same patient were made with the leg dependent, using the apparatus as an air and a fluid plethysmograph. The resting flow values in the air plethysmograph were 1.8 to 7.0 c.c./min./100 c.c. limb volume, and in the fluid plethysmograph they were 1.3 to 4.0 c.c./min./100 c.c. limb volume. The maximum flows during reactive hyperemia were, respectively, 9.6 and 10.6 c.c./min./100 c.c. limb volume for the air- and for the fluid-containing plethysmographs.

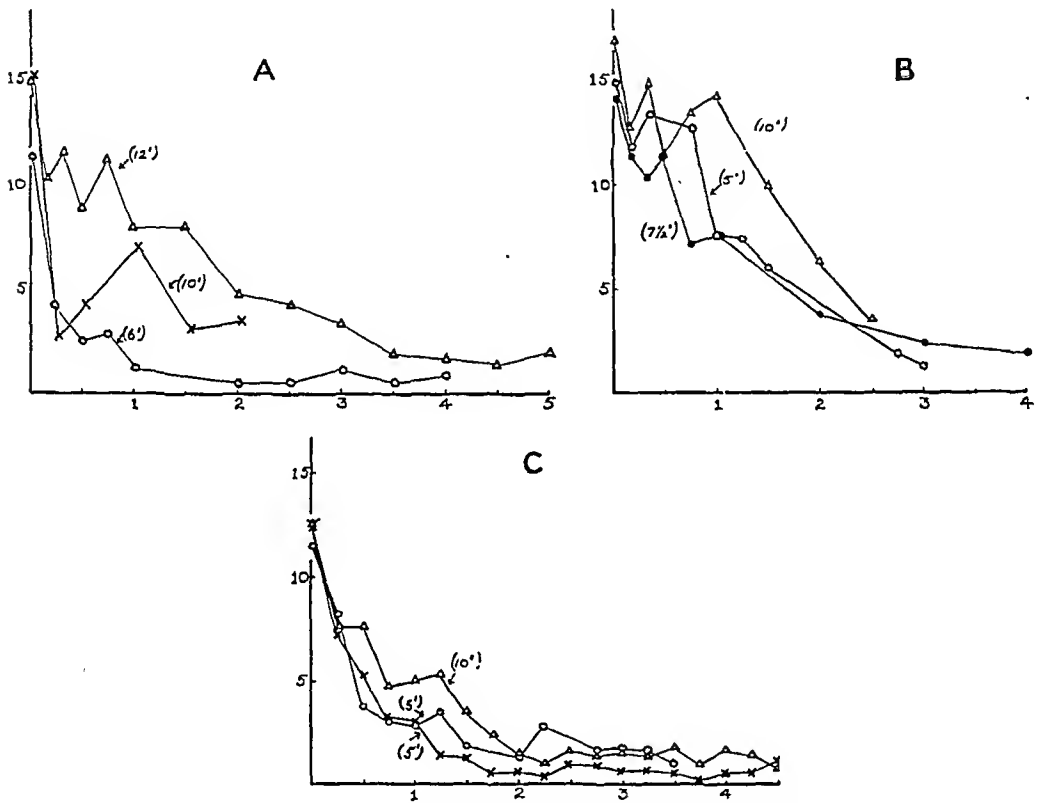


Fig. 10.—Time course of rate of blood flow in foot and leg after release of arterial occlusion, showing extent and subsidence of reactive hyperemia in three normal subjects. Abscissae indicate time in minutes; zero time is the moment of release of arterial occlusion; ordinates indicate blood flow in c.c./min./100 c.c. limb volume. The duration, in minutes, of arterial occlusion preceding each curve is shown in parentheses.

In a number of cases comparative measurements were made of the maximum flow during reactive hyperemia after arterial occlusion with the maximum flow when the leg was warmed to 43° C. for thirty minutes or longer.\* In one case the flow at 43° C. was 7.5 c.c./min./100 c.c. limb volume, as compared to 6.4 c.c./min./100 c.c. limb volume during "reactive hyperemia." In another case (Fig. 11) the maximal flow during reactive hyperemia was 10.8 c.c., on heating it was 8.0 to 13.1 c.c., and on inducing reactive hyperemia in the heated leg it was 10.5 to 14.6 c.c.

Our values for resting and maximal flows in the normal limb in the horizontal position are of the same order as those reported in the litera-

\*Some question might be raised as to the comparability of heating a leg in an air bath and a water bath. It has been stated that there is a difference in effectiveness in producing reflex vasodilation.<sup>34</sup> Our maximum of flow in the air-heated limb corresponds fairly well with the results obtained by heating in a water bath.

ture (Fig. 11). Abramson, et al.,<sup>17</sup> reported flows of 1.3 to 6.6 c.e./min./100 c.e. limb volume at 32° C., and 9.9 to 17.2 c.e./min./100 c.e. limb volume at 45° C., and, in another study, 1.4 to 5.5 c.e./min./100 c.e. limb volume at 32° C. and 9.8 to 25.5 c.e./min./100 c.e. limb volume at 45° C.<sup>35</sup> Kunkel and Stead<sup>36</sup> reported maximal flows at 43° C. of 11.1 to 25.9 c.e./min./100 c.e. limb volume. Five minutes of arterial occlusion did not increase the flow in the heated extremity in two patients, whereas in a third the flow increased from 22.9 to 26.4 c.e./min./100 c.e. limb volume. Wright and Phelps<sup>18</sup> reported, for a large volume of leg, a resting flow of 1.8 to 4.2 c.e./min./100 c.e. limb volume, a maximal flow, after heating, of 6.9 to 8.0 c.e./min./100 c.e. limb volume, and, after heat and sacral diathermy, of 11.7 c.e./min./100 c.e. limb volume.

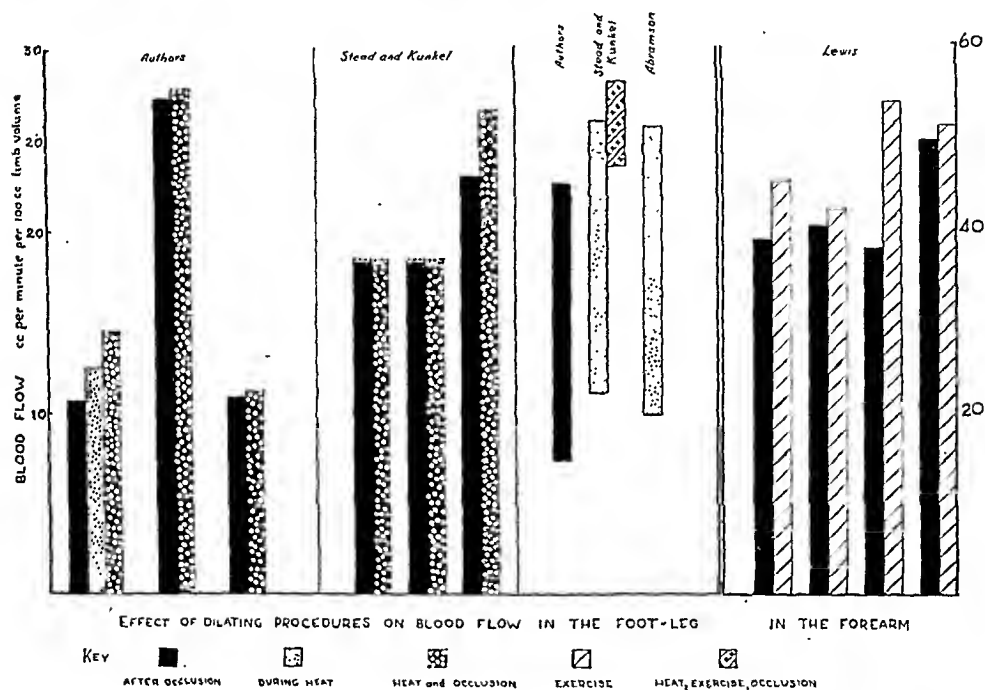


FIG. 11.—Effect of various dilating procedures on blood flow in the foot-leg and in the forearm. Our results were obtained in the present study; see Kunkel and Stead,<sup>36</sup> Abramson et al.,<sup>35</sup> and Lewis and Grant.<sup>29</sup>

In the studies of Killian and Oelassen,<sup>37</sup> the recorded blood flow in the foot at room temperature was 0.9 to 4.2 c.e./min./100 c.e. limb volume, and, after dilatation by local heat and a hot mustard bath, the values were 6.4 to 14.8 and 7.3 to 13.2 c.e./min./100 c.e. of limb volume,\* respectively.

Our results also confirm the amply demonstrated observation<sup>1, 9, 20, 31, 37-39</sup> that there is a general correlation of resting flow with local or environmental temperature.

Although there is no precise correlation of limb blood flow with age,<sup>36</sup> the resting flow appeared to be less in the younger subjects of our series. It must be noted, however, that the oldest subject was only 40 years of age.

\*Data given, or calculated by approximation from data given.



Our results, which indicate that the maximum flow in the resting dependent limb is less than that in the horizontal limb of the same and of other patients, are in keeping with other evidence that the flow to the dependent limb is reduced.<sup>40, 41</sup> This may be because the cardiac output is less in the sitting than in the lying position<sup>42-46</sup>—although this observation has been questioned<sup>47, 48</sup>—or because of congestion of the dependent vessels<sup>43, 49, 50</sup> and/or a diminution of circulating blood volume.<sup>51</sup>

In the sitting position, hydrostatic pressure up to the height of the blood column (of the order of 50 mm. Hg) is thrown upon the arteries and veins of the limb, and distends them.<sup>50</sup> This is compensated for to some extent by an alteration in the general systemic blood pressure level.<sup>51</sup> The hydrostatic pressure would nevertheless operate to increase intramuscular tension in the dependent leg, to distend the leg and its blood vessels, and thus to increase the cross-section area of the vascular bed. The net effect would be greater resistance to the inflow of blood to the leg, as well as greater opposition to passive or active constriction of the blood vessels of the leg. The pooling of blood in the dependent parts could decrease the venous return, the circulating blood volume, and the cardiac minute output, all of which would further tend to reduce the blood flow. The resting flow could be maintained unchanged by compensatory dilatation, but the existing differences might be indicated by comparing the fully dilated vessels.

Apparently because of the balance and variation of the factors in operation, we were unable to demonstrate a difference of resting flow in the two positions beyond the limits of error of the method, but a difference in flow was demonstrable with the vessels fully dilated by heat or reactive hyperemia (Fig. 9).

Before our results are taken to indicate confirmation of the foregoing concept, it must be ascertainable whether the method is as reliable for the dependent as it is for the horizontal leg. The same conditions which act to reduce blood flow may also limit the validity of the method of measuring blood flow. These factors are elevation in venous pressure and distention of the veins and tissues of the limb. The elevation of the venous pressure caused by dependency of the limb may prevent complete occlusion of the veins when the collecting cuff is applied, and the presence of more distended veins and a more distended leg may make the resistance to further distention greater. In order to rule out these possibilities, the distention and increased venous pressure which occur in the dependent leg were reproduced in the horizontal leg by congesting the limb prior to, or during, the arterial occlusion. This maintained an increased venous pressure but did not interfere with the development of the resultant hyperemia.<sup>29</sup> Under these circumstances, the initial flow was sometimes found to be less (Fig. 12) and the maximum inflow to occur later than in those experiments without venous congestion. The presence of congestion at the start offered resistance to inflow, but, with the release of the arterial obstruction, the conges-

tion was quickly relieved because the venous occlusion was also removed, and the limb volume therefore decreased. As the inflow increased it tended to cause an increase in leg volume, as it did in the uncongested limb, but this increase was delayed or masked by the pre-existing congestion.

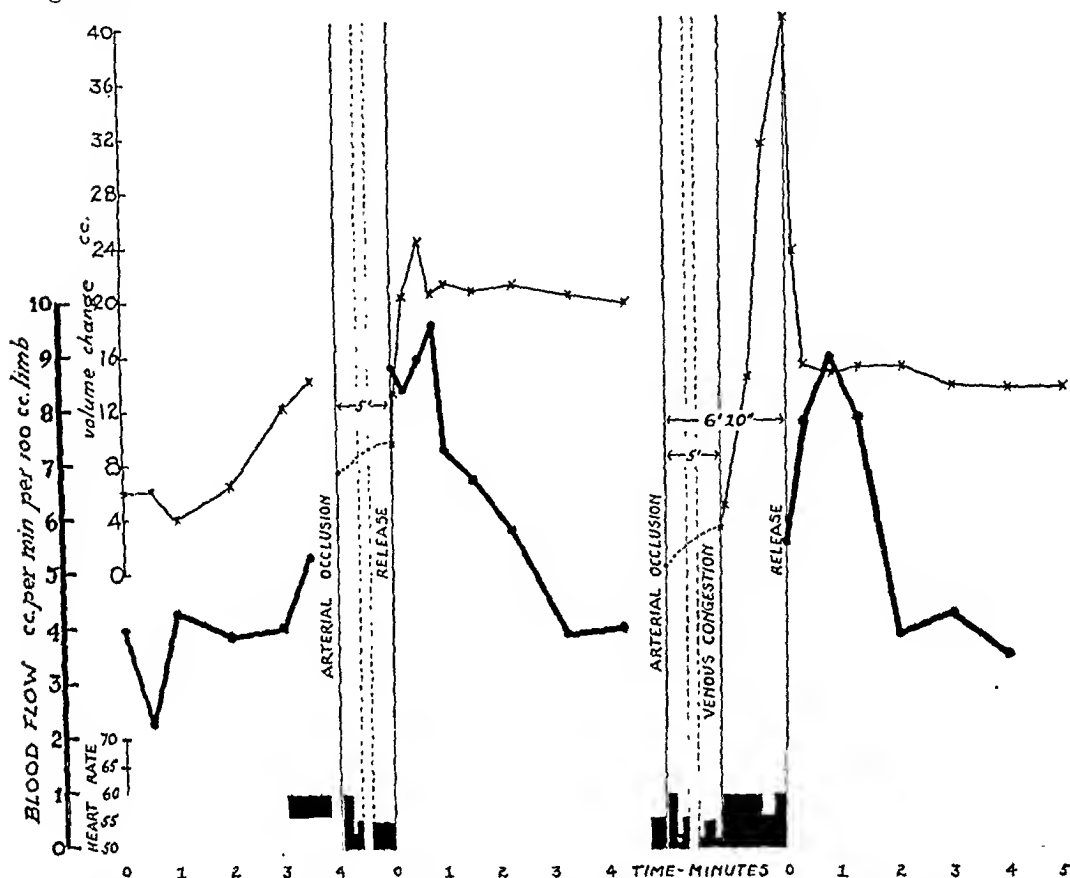


Fig. 12.—Effect of release of arterial occlusions of like duration with and without venous congestion. Blood flow is represented by the heavy line; relative limb volume, by the light line; and heart rate, by blocks.

This alteration of flow as a result of congestion may explain how, in a previously uncongested limb, a temporary decline in blood flow occurred in some instances during reactive hyperemia (Figs. 10 and 12). When the arterial occlusion was released in an uncongested leg, blood entered the leg faster than it could leave, with the result that the leg volume increased (Fig. 12) and the pressure in the small vessels and veins rose.<sup>52</sup> This, in turn, offered resistance to further flow, which might have resulted in a decline in the rate of inflow when the limb volume was at a maximum. On the other hand, the congestion and rise of venous pressure themselves led to acceleration of outflow, thus relieving the hindrance to inflow; at the same time, the pulse acceleration resulting from the release of arterial occlusion (Fig. 12) indicated a temporary increase in cardiac output which tended to increase inflow above normal. These two factors, therefore, caused the initial decline to be temporary, and therefore to appear as a notch on the curve of

flow (Figs. 10 and 12). Intermediate degrees of congestion or venous pressure elevation may be expected to effect similar trends. The increased venous pressure produced by deliberate congestion quickly disappeared after release, whereas that in the dependent leg, because of its position, was constant.

It is indicated by these experiments that (a) congestion of a limb, per se, decreases inflow, and this can account for the decreased maximum flow in the dependent limb, and (b) the presence of congestion makes observation by this method less reliable, and therefore more accurate data on resting and maximum flows are to be obtained in the uncongested limb than in the congested one. However, the degrees of venous pressure elevation deliberately produced in the experiments with congestion were much greater than might be expected under ordinary clinical conditions of increased venous pressure. Nevertheless, optimal conditions require low venous, tissue, and environmental pressure, and therefore the use of a horizontal position of the leg near the level of the heart. We do not think that the decreased flow in the dependent leg, the initially low flow in the congested leg after release of arterial occlusion, and the transient decrease in flow in the uncongested leg after release of arterial occlusion are reliably quantitated by our measurements.

It has often been pointed out that maximum flow is a better measure of the vascular status of a part than is "resting flow."<sup>36</sup> The resting flow is determined largely by the amount of vasoconstriction caused by humoral, physical, or neurogenic influences. Most workers have used heat to produce maximal flow. Our selection of reactive hyperemia was deliberate because we were interested, in part, in the study of its mechanism.

Our values for maximal flow in the normal leg-foot in the horizontal position are of the same order of magnitude as those reported by other workers who studied similar subjects, but employed heat to produce maximal flow (Fig. 11). Heat, whether used alone or in combination with reactive hyperemia, gave slightly greater flow than reactive hyperemia alone, both in our experiments and in those reported by others. Other dilating agents have produced no greater flow.<sup>37, 53, 54</sup>

Heat and reactive hyperemia do not operate in an identical manner. In the leg-foot we are dealing with the flow in both skin and muscle. Heating an extremity to 43° C. for thirty or more minutes produces dilatation primarily of the skin vessels.<sup>23</sup> The deeper vessels are not dilated; in fact, muscular vessels may be constricted. Apparently, all the skin vessels participate in this dilatation, viz., A-V shunts,<sup>55</sup> arterioles and venules, probably the arteries, and perhaps the veins. The dilatation involves not only the locally heated vessels, but also the skin vessels throughout the body as a result of a reflex mediated by sympathetic cutaneous nerves.<sup>56, 57</sup> Consequently, there are changes in blood distribution, blood pressure, and cardiac output. The dilatation re-

quires a certain amount of time to reach a steady state and disappears slowly. The function of the circulatory adjustments in this case is temperature regulation. Other functions of the circulation—the transport of metabolites—are not primarily involved. In fact, the dilatation of A-V shunts in the skin may actually decrease the blood flow through the “working” capillaries of the tissues.

The advantages of the use of heat are the tolerance of most subjects to it, the ease of its production, and the fact that it can be maintained to get check readings. The disadvantages consist in the alteration of the normal conditions of the limb, in the time (about one-half hour) required to reach a steady state, in the difficulty of maintaining controlled heating in an air-system plethysmograph, in the intolerance of some patients to it, in the variability of response to it among patients, and the limitation that the dilatation produced is primarily in skin vessels.

On the other hand, during reactive hyperemia after occlusion, the smaller arterioles and the capillaries and venules of the entire extremity are dilated.<sup>23</sup> An increase in heart rate and a change in blood pressure occur.<sup>53</sup> The blood flow of the opposite extremity is, however, not significantly affected. Reactive hyperemia results from anoxia, and the increase in flow is the means by which the oxygen debt is quickly repaid. The advantages of the reactive hyperemia method are that the dilatation is more widely distributed in the limb, observations may be made and repeated with ease and speed, normal rate of flow soon returns, and generalized alterations in circulation do not occur. The disadvantages are occasional pain and discomfort, interference with limb nutrition, and the transient character of the dilated state which is produced.

Increasing the duration of the occlusion resulted in an increase in the maximal flow after release of the occlusion. The relationship between the duration of occlusion and maximum flow is presented graphically in Fig. 13 for our results and for the results published by Lewis and Grant.<sup>29</sup> The maximal flow did not increase proportionately as the duration of occlusion was increased, but approached a limiting value. This limiting maximal flow was obtained by occlusion for ten to fifteen minutes, and indicates that about 80 per cent of the maximal flow may be reached after release of occlusion which has been maintained for five to ten minutes. Shorter and repeated periods of reocclusion, if promptly applied after release of a longer occlusion, also produced a high maximal flow upon release.\*

One or more of three factors may impose a limit upon this maximal flow: (a) when the occlusion is maintained beyond the optimum time, constricting factors may limit the effective dilatation; (b) as the occlusion is prolonged, the vessels may reach the maximum extent of their dilatability, both as regards degree and number of vessels; and (c) it

\*Contrary conclusions were drawn from work on anesthetized animals,<sup>50</sup> but they were based on limb volume observations, not on blood flow measurements.

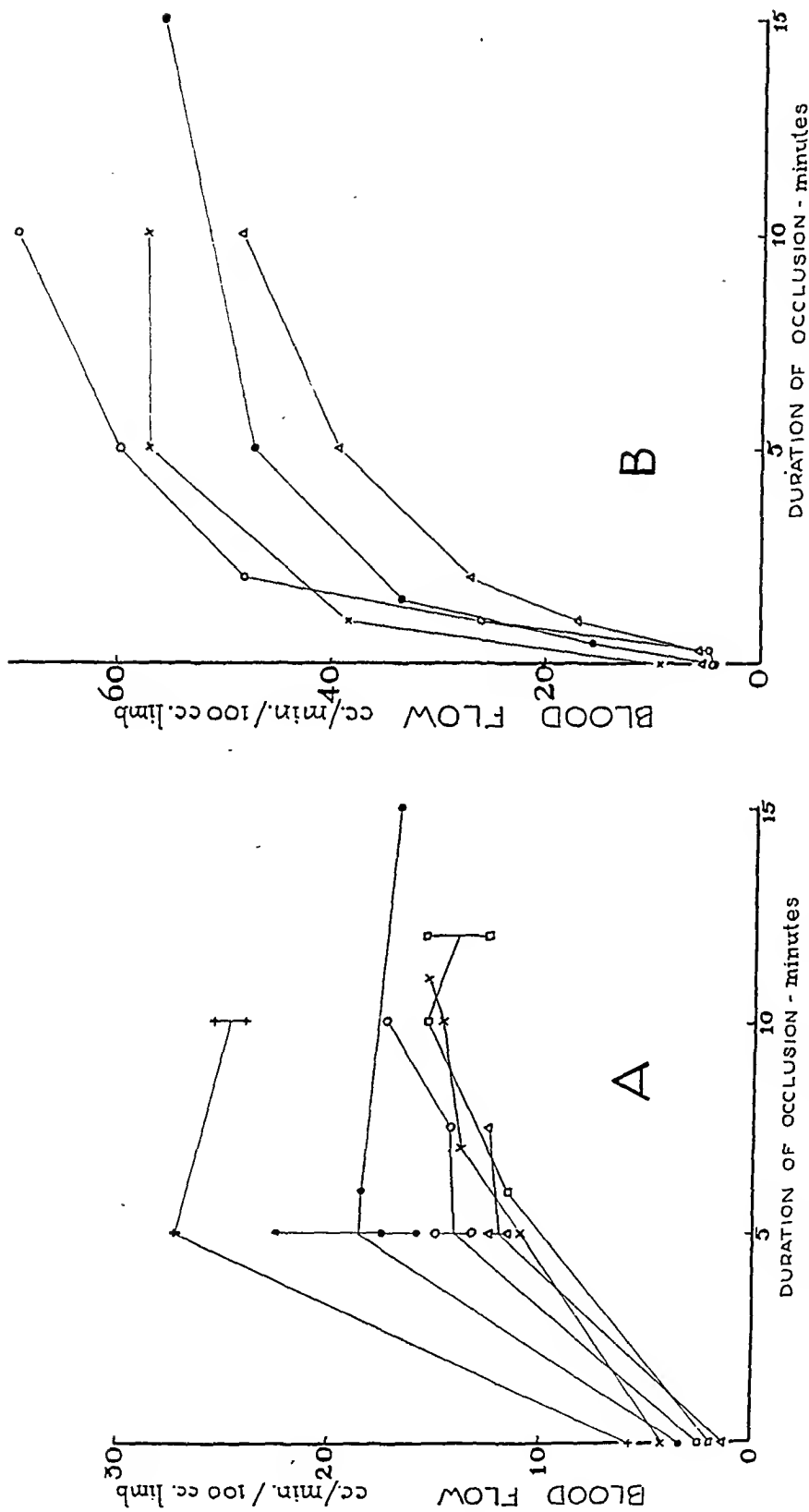


Fig. 13.—In A are plotted our results on the relation of maximum flow in the foot-leg after release of arterial occlusion to the duration of this occlusion. In B are plotted the data of Lewis and Grant <sup>20</sup> on the relation of blood flow in the forearm at the moment of release of arterial occlusion to the duration of such occlusion.

should be recognized that, as the dilatation is increased beyond a certain point, the resistance offered by the larger vessels, or at least by vessels not participating in the dilatation, becomes proportionately greater, until the limit of flow may be determined primarily by the caliber of these vessels, rather than by those which are being dilated.

As regards the use of other dilator agents, the experiments of Wright and Phelps<sup>18</sup> are applicable. Maximum flows as a result of using heat alone were as great as those obtained by any combination of methods with heat, and were approached only by the values after nerve block. In their studies, sciatic block, spinal anesthesia, diathermy, and reflex and local heat were used. Kunkel and Stead<sup>36</sup> reported that heat plus arterial occlusion, and both plus exercise, resulted in flows in the foot which were little, if any, greater than those produced by heat alone. Applying heat to the forearm<sup>29, 36</sup> did not produce maximal dilatation in this region. This was attributed to the relatively small proportion of skin in the vascular area of the forearm. Arterial occlusion and exercise, or both, yield about the same maximal flow in the forearm.<sup>16, 53, 60\*</sup>

This evidence indicates that the maximum flow in the foot-leg is of the same order of magnitude, although produced by diverse means. It is hardly likely that all the peripheral vessels dilate to the same degree under each of these conditions. It is more probable that some other factor limits the maximum rate of flow. This could be the cross-section area of the central arteries. The principle of continuity of flow, which predicts that the amount of flow in one section of a system of tubes equals that in the preceding section when conditions are stabilized, applies here. Under a given driving force (the arterial pressure), there is a limit to the amount of flow which can pass a given point in the central artery, and this might be considerably less than the amount which could pass through the dilated vessels beyond. If this be true, when the resistance in the peripheral vessels falls below this level, the factor determining flow will become the cross-section area of the feeding artery to that region. An analogy may be drawn to a plumbing system in which water flows from a main through an inlet pipe to be distributed to a household. When most of the faucets are closed, the flow from the main to the inlet pipe is determined by the number of open faucets. As more and more are opened, a point may be reached at which the factor limiting flow in the inlet pipe is the cross-section area of the pipe itself. At this point, even if more faucets are opened, no significantly greater flow can occur. Whether or not this happens, and the point at which it occurs, depend upon the relative size of the inlet pipe and the size and number of the faucet openings. To carry the analogy further, when pipe corrosion occurs or scale is deposited in the inlet pipe, the maxi-

\*Since a distal occluding cuff about the wrist and ankle is used in measuring forearm and calf flow, it would be desirable to examine the method critically in this instance before accepting the results unreservedly.

mum amount of water that can be drawn per unit of time will be decreased. This concept is of some importance in understanding the usefulness of maximal flow, for it shows that, under certain circumstances, maximum flow may not measure the maximum dilatation of peripheral vessels, but may measure, instead, the cross-section area of the artery to the part. It may explain why maximal flow in the normal leg and foot is obtained by dilating only skin vessels with heat, as well as by dilating all the small vessels with reactive hyperemia. *Variations in maximal flow under different circumstances may therefore mirror changes in systemic pressure (driving force), express changes in peripheral resistance in the small vessels, or indicate alterations in central arterial caliber.* Flow varies directly with pressure and inversely with total resistance (in series).

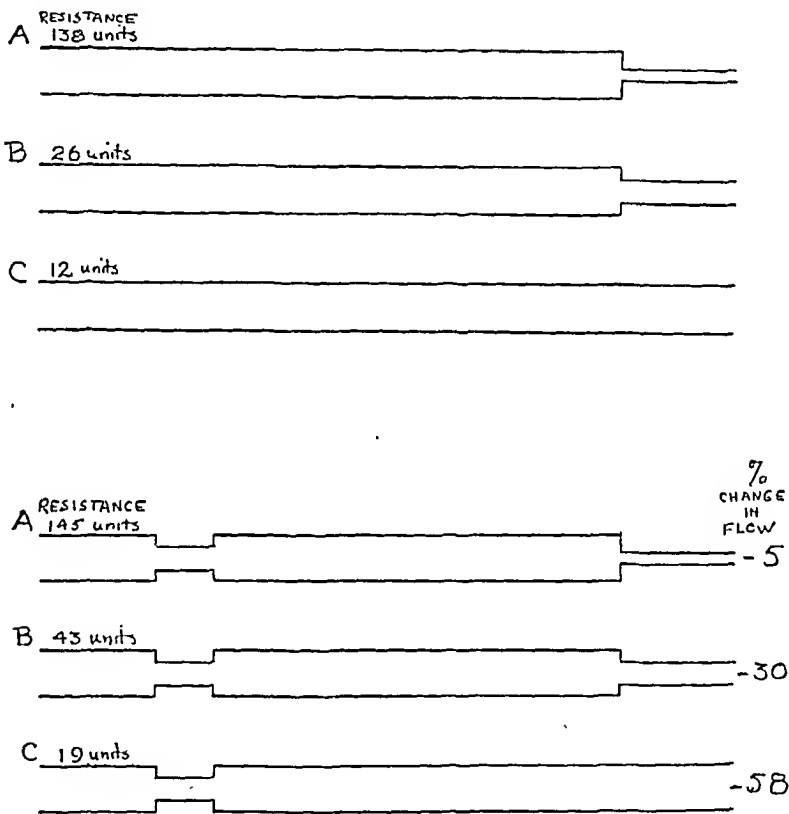


Fig. 14.—Upper set of diagrams represents the same central vessel with three different degrees of peripheral vascular caliber. Lower set of diagrams represents the effect of equal constriction of this central vessel upon the flow through the above three vessel systems. On the right-hand margin is shown the percentage change in inflow. Discussed in text.

This concept, in corollary form, can also be applied to the effect on blood flow of progressively decreasing the caliber of an artery. This has been done in a number of ways. Mann, et al.,<sup>61</sup> found that, in the carotid artery of the dog, a 50 per cent reduction in the lumen could be produced without any change in blood flow, and that a 90 per cent constriction was necessary before a 50 per cent decrease occurred. When graduated, partial compression was applied to the cat's pulmonary

artery,<sup>62, 63</sup> dynamic alterations indicative of significant changes in blood flow appeared only after the diameter had been reduced 52 to 66 per cent. In models, Mann, et al.,<sup>61</sup> found that a 40 per cent reduction in the diameter of the central tube was required to reduce the flow. It should be appreciated that such experiments do not demonstrate the effect of narrowing a vessel upon flow as much as they illustrate how much central constriction is required to make the total resistance significantly greater than the peripheral resistance had been. In the experiments with animal vessels and models, mentioned above, the true effect of narrowing the major artery, i.e., the relation of flow to cross-section area, would have been demonstrated only if there were full peripheral dilatation. This can be illustrated by certain approximations.

In the upper set of diagrams of Fig. 14 a system of tubes represents the arterial tree. A segment 10 units in length represents the central vessel, and a segment 2 units in length represents the peripheral vessels. This is illustrated under three hypothetical circumstances in *A*, *B*, and *C*, in which the segments which represent compositely the small vessels are indicated, respectively, with radii  $\frac{1}{4}$  of,  $\frac{1}{2}$  of, and equal to, that of the central vessel. If each unit of length of the central vessel has a resistance of 1, the entire resistance of the central vessel is 10 in each case. The resistance of the peripheral vessel increases as the radius is decreased, and is inversely proportional to some power of the radius between the square and fourth power. For purposes of illustration, the resistance may be considered to vary inversely approximately as the cube of the radius. Therefore, the resistance in the peripheral vessel in *A*, *B*, and *C* of the upper part of Fig. 14 will be 64, 8, and 1, respectively, per unit length. The net resistance of the tubes illustrated will be 138, 26, and 12.

Now let us note the effect of constricting one unit of length of the central vessel to half its diameter in each case, as illustrated in *A*, *B*, and *C* of the lower part of Fig. 14. The central artery resistance is now 1 unit of 8, plus 9 units of 1, or 17, instead of 10, as was the case before. The net effect is to increase the resistances of *A*, *B*, and *C* to 145, 43, and 19 units, respectively. The change in resistance in tubes *A*, *B*, and *C* between the upper and lower parts of Fig. 14 therefore amounts, respectively, to 5 per cent, 30 per cent, and 58 per cent, although the same amount of central constriction had been applied to each in each instance. It is thus apparent that the effect of constriction of a vessel upon the flow through it (with constant inflow pressure) depends not only on the size of that vessel, but also upon the state of the entire system through which the flow occurs.<sup>64</sup> Dilatation of the peripheral vessels makes each central segment relatively more important in its contribution to the total resistance to flow.

The maximum flow may thus be taken to indicate the caliber of the vessels supplying the part, if it appears that, with full dilatation of the peripheral vessels, the diameter of supplying vessel is the limiting



factor in the level of flow attainable. This concept has a certain bearing on disease. Since maximal flow is dependent upon arterial pressure, the "maximum flow" should be greater in hypertension, regardless of cause, unless a certain degree of peripheral resistance, irreversible by whatever dilating method is used, is present as the result of the process leading to hypertension. In peripheral vascular disease, maximal flow studies would indicate reduction of major arterial lumen, as well as the presence of peripheral vessel involvement irreversible by a dilating stimulus. They would not give any indication of distribution of blood flow to various parts of the limb according to needs, for redistribution of flows would not be indicated. Especially is this so because a large part of limb flow is to the skin. Since maximal flow may be thus limited by the caliber of central vessels, the relative merits of peripheral vasodilator procedures cannot be evaluated if these procedures dilate peripheral vessels beyond a point at which the calibers of the more central vessels become appreciable, effective, limiting factors to flow. In this event, their effect can be judged only by the speed and persistence of their action, or by the use of smaller doses. Maximal flow may be conditioned by any effect that the peripheral dilating agent has upon large vessels. Heat may dilate arteries,<sup>23</sup> and the application of occluding cuffs may evoke arterial narrowing.

The importance of recognizing the limitation of flow imposed by a vascular segment applies to all regions of the body in health and disease. It is quite possible that, in some localities, even with full peripheral dilatation, no significant shift occurs in the distribution of effective resistance, and that, in others, even normally, the limiting factor of resting flow is the caliber of the central artery.

#### SUMMARY AND CONCLUSIONS

The theory and technique of the plethysmographic method of measuring blood flow are critically presented.

When the magnitude of errors which cannot be eliminated is known, much valuable information may be obtained if the limitations of the method are appreciated, and if results are carefully interpreted.

An adequate apparatus for studying the volume of blood flow in the human foot-leg is described.

Values for resting and maximal volume flows on normal subjects are given, and their interpretations discussed. Arterial occlusion as a method of producing dilatation resulting in maximal blood flow was studied.

Evidence is presented to indicate that, under certain circumstances, the caliber of central vessels may be the principal factor which determines the "maximal" volume of blood flow to a region.

Throughout this work the authors received invaluable assistance from Dr. Kenneth Jochem, especially with mechanical and mathematical problems.

The results of our study and those of Wilkins and Eichna (Bull. Johns Hopkins Hosp. 68: 425, 1941), which were published after the conclusion of this work, are in agreement, especially as regards their extensive observations on reactive hyperemia. Their studies further support the concepts underlying peripheral flow that we have attempted to present.

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## THE INTERNAL PNEUMOCARDIOGRAM\*

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*Definition.*—The term “pneumocardiogram” is here applied to the tracing of the pressure changes which occur in the air passages of the lungs as a consequence of the heart beat.

Previous terms for the same phenomenon include the following: “negative thoracic pulse,” “cardiopneumatic waves,” “respiratory pulse,” “heart notchings,” and “heart interruptions of the respiratory curve.”

*History.*—Old physiologic studies showed that the heart beat is accompanied by changes of pressure within the thorax. The heart beat causes a movement of air through the upper respiratory passages which, under normal conditions, is not accompanied by any perceptible sound. In the presence of disease, however, the air movement through the nostrils and mouth may be affected by the heart in such a way that the observer becomes aware of it, and there may even be a subjective sensation, which may account for many early studies on patients.

*Clinical Studies.*—The first clinical observations were made between 1867 and 1888 by Friedreich,<sup>1</sup> Galvagni,<sup>2, 3</sup> and Cheesmann,<sup>4</sup> who were followed, in later years, by Gerini,<sup>5</sup> Fiseher,<sup>6</sup> Binetti,<sup>7</sup> and Lang.<sup>8</sup> Evident tracheal or oral murmurs with a cardiac rhythm were described by these authors in many diseases, especially in connection with aortic insufficiency and aortic aneurysm. The important contributions of Galvagni on “oral auscultation” should be mentioned, and also the name “oral whiff,” coined by Cheesmann.

*Graphic Studies.*—In 1861, Buisson<sup>9</sup> described, after animal experimentation, the so-called “negative thoracic pulse” caused by the decrease in the volume of the heart as a result of ventricular systole. Bert<sup>10</sup> studied from the trachea the rhythmic oscillations due to the movements of the heart. Landois,<sup>11</sup> in 1876, obtained records of air pulsations from the mouths of normal people. He described *negative waves* which occurred when the glottis was open (cardiopneumatic waves), and *positive waves* when the glottis was closed. The latter were

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\*The term “pneumocardiogram” has been recently employed by H. A. Blair and A. M. Wedd (AM. HEART J. 17: 536, 1939). They make use of this term with reference to the rapid changes of chest volume caused by the heart beat. Their records and mine register essentially the same phenomena. However, inasmuch as the techniques were not the same, and the results are probably also different, it would avoid confusion to call my records “internal pneumocardiograms.” This implies that there is a direct connection between the recorded waves and the intrapulmonary pressure. The records of Blair and Wedd should be called “external pneumocardiograms.”

due to the pulsation of the bucepharyngeal vessels when the mouth and pharynx became a closed cavity as a result of closure of the glottis.

Two years later, Mosso<sup>13</sup> studied, by means of Marey tambours, eardiopneumatic tracings on man, and described a *double-notched systolic wave* due to a systolic diminution of the pressure in the thorax. He attributed the first notch to dilatation of the thorax caused by the apex beat, and the second to the diminution of heart volume. However, his records, which were reproduced by Lueiani in his textbook,<sup>14</sup> do not confirm this explanation.

The successive researches of Klemensiewicz<sup>15</sup> and of Haykraft and Edie<sup>16</sup> led to the conclusion that the chief part of the pulsations was due to rhythmic compression of the lung by the heart apex. This conclusion seemed to be supported by the fact that opening the thorax did not abolish the pulsations. François-Frank,<sup>17</sup> however, attributed the persisting waves to the pulsation of the pulmonary vessels, which could not be recorded when the thorax was closed.

The technique of making graphic records from the nose was later applied to patients by Siciliano,<sup>18</sup> Cremer and Matthes,<sup>19</sup> and Frugoni.<sup>20</sup> In their cases only a single negative wave was described, but it had quite a marked intensity.

In 1918, Klewitz<sup>21</sup> gave a description of many more details of the cardiac waves of the respiratory curve. He described a small negative wave during auricular systole, and a large negative wave during ventricular systole. Between the two a small positive notch was present, and another was found at the time of closure of the aortic valves.

*Pneumotachographic Studies.*—A third phase started with the description of the pneumotachograph, an apparatus which enables one to study the velocity of air flow during normal respiration. Fleisch<sup>22</sup> and his co-worker, Bretsehger,<sup>23</sup> gave all details of physiologic pneumotachograms.

In 1928 I observed a group of normal people and cardiac patients and studied the heart waves of the respiratory curve, employing the Fleisch pneumotachograph, as well as the older technique, modified by the use of a Frank capsule.<sup>24</sup>

These studies demonstrated that the waves caused by the heart beat are quite similar in both records. They are quicker in the pneumotachogram, and slower, but often more evident, in the pressure records. A real retrogression of the air stream takes place only when systole occurs in the phase between inspiration and expiration. Otherwise, the waves due to the heart beat cause only a diminution of speed.

At that time I described three chief negative waves: (1) a presystolic wave coinciding with auricular systole ("a" wave), (2) a systolic wave coinciding with ventricular systole ("v" wave), and (3) a diastolic wave following the closure of the aortic valves ("d" wave).

The possibility of positive waves between the negative depressions was not excluded. A marked increase of the auricular a wave in mitral

valve defects and of the ventricular *v* wave in aortic insufficiency and hypertensive patients were the chief results of my clinical studies.

The necessity of avoiding closure of the glottis was confirmed by the high positive pulse which sometimes occurred in less trained patients if they were asked to hold their breath.

A year later, Hochrein and Weiss<sup>25</sup> studied, by means of the Hochrein pneumotachograph, the pulsations of the air column which are caused by the heart beat. They found small notches on the respiratory curve, but studied them only during inspiratory or expiratory standstill. No definite notchings were observed by them in normal people during respiratory standstill. Notchlike elevations were found in both inspiratory and expiratory standstill in patients with aortic aneurysm, but only during the inspiratory standstill in patients with adhesive pericarditis. The study was extended later by Hochrein<sup>26</sup> and by Hochrein and Laplace<sup>27</sup> on patients with adhesive pericarditis and on experimental animals. The technique of these studies and their results were discussed by Fleisch,<sup>28</sup> Holzlöhner,<sup>29</sup> Hitzengerger and Hinteregger,<sup>30</sup> and Luisada.<sup>31</sup>

In 1935 and 1936, some new physiologic and clinical studies were published by me<sup>31-33</sup> and by my co-worker, Rubino.<sup>34</sup> Rubino recorded simultaneously the intrathoracic pressure on the right side and the nasal tracing and found an absolute similarity of details. This eliminated any possibility that the apex beat is a causative factor.

Among the chief clinical results of these studies should be mentioned (a) the tremendous increase in size of the systolic *v* wave in aortic insufficiency,<sup>32, 34</sup> (b) the increase of all waves, but chiefly of the auricular *a* wave, in patients with mitral disease,<sup>32, 34</sup> and (c) the gigantic negative wave, followed immediately by a positive one, which occurs during systole in patients with tricuspid insufficiency.<sup>31, 32</sup>

*Later Studies.*—The most recent studies were carried out on normal people by Holzlöhner.<sup>35, 36</sup> This author studied the records obtained by the pneumotachograph and the dielectrograph, and pressure curves from the mouth. By using the pneumotachograph with a string anemometer, he obtained much clearer details of the curve. In the recumbent position the chief deflection is a downward early systolic wave, which is followed by a small upright and a second small downward systolic wave. A small presystolic and a small diastolic wave are also present. Marked modifications, either following changes in position, or due to the difference between expiratory and inspiratory standstill, were also described by him. He explains all the recorded waves by the difference between inflow to, and outflow from, the thorax, and excludes any change caused by either the apex beat or diaphragmatic pulsations.

The changes due to position and to respiratory phase were explained by the unlike action of the systolic aspiration on the large veins, in

which a different tension occurs. The changes dependent upon position should be known in order to be able to use a uniform technique.

Comparative studies of different methods showed Holzlöhner that the pressure curves were more like air velocity tracings than volume curves, but had something in common with both. No fundamental difference was found between pressure and air velocity curves, and all the typical points of inversion of the waves were found to be identical.

### TECHNIQUE

I have endeavored to find a new and easy technique which could reproduce all details of the pneumocardiogram and enable the physician to use this kind of tracings routinely. I have avoided, therefore, every technical device (pneumotachograph, mask), and everything else (special position, mouth tube, respiratory standstill) which requires special training of either the physician or the patient.

*Apparatus.*—I have used a Sanborn Stetho-Cardiette<sup>37</sup> for the simultaneous registration of the pneumocardiogram and the heart sounds. A comparison of the pneumocardiogram with the phonocardiogram permits an analysis of the component waves of the former. A Sanborn piezoelectric microphone, such as is usually employed for sphygmographic purposes,<sup>37, 38</sup> was also used. To this I added a high-pass filter for decreasing the intensity of the slow respiratory deflections without curtailing the quick pulsations caused by the heart beat. The plug of the sphygmographic microphone is inserted into the filter, and the plug of the filter is inserted into the electrocardiograph. A control arrangement on the filter is used for varying the degree of attenuation upon the slow respiratory deflections. Some experiments were performed in which three simultaneous registrations were employed. The apparatus for this purpose was the Sanborn Tri-Beam Stetho-Cardiette.<sup>37</sup>

*Tracing and Standardization.*—A rubber tube, 10 inches long, is connected to the microphone. It ends in a bakelite olive which is inserted into one of the nostrils of the patient. The patient is placed in a comfortable sitting position, with complete muscular relaxation. A semirecumbent position may also be employed. The physician must instruct the patient to breath normally through the nose (with the mouth closed).

With the above-described arrangement, the pneumocardiogram is registered in a manner similar to that for an electrocardiographic lead. During the normal breathing of the patient two operating adjustments may be made: (1) the degree of filter attenuation upon slow respiratory waves, and (2) the registration sensitivity of the electrocardiograph. By regulating both, the physician can obtain a tracing in which the waves will be from 1 to 2 cm. high, and even the extreme phases of respiration will be recorded within the limits of the sensitized paper. The pneumocardiogram is normally registered at a paper speed of 75 mm. per second.

A mechanism\* was employed for the standardization of the pneumocardiographic deflections. This is merely a device which produces a known change of pressure in the pneumocardiographic tube which is connected to the patient's nostril. The pneumocardiographic deflections may then be expressed in millimeters of water if none of the conditions of the experiment were changed.

The above-described technique has the following advantageous characteristics: (a) possibility of accomplishing the work with a commercially obtainable apparatus,

\*Supplied by the Sanborn Co.



(b) no special training required on the part of the patient, and (c) correct registration of every slight change of pressure of the air caused by the heart beat.\*

#### DESCRIPTION AND EXPLANATION OF THE RECORDS

The average pneumocardiogram possesses a typical characteristic which will now be described. It has, fundamentally, five negative

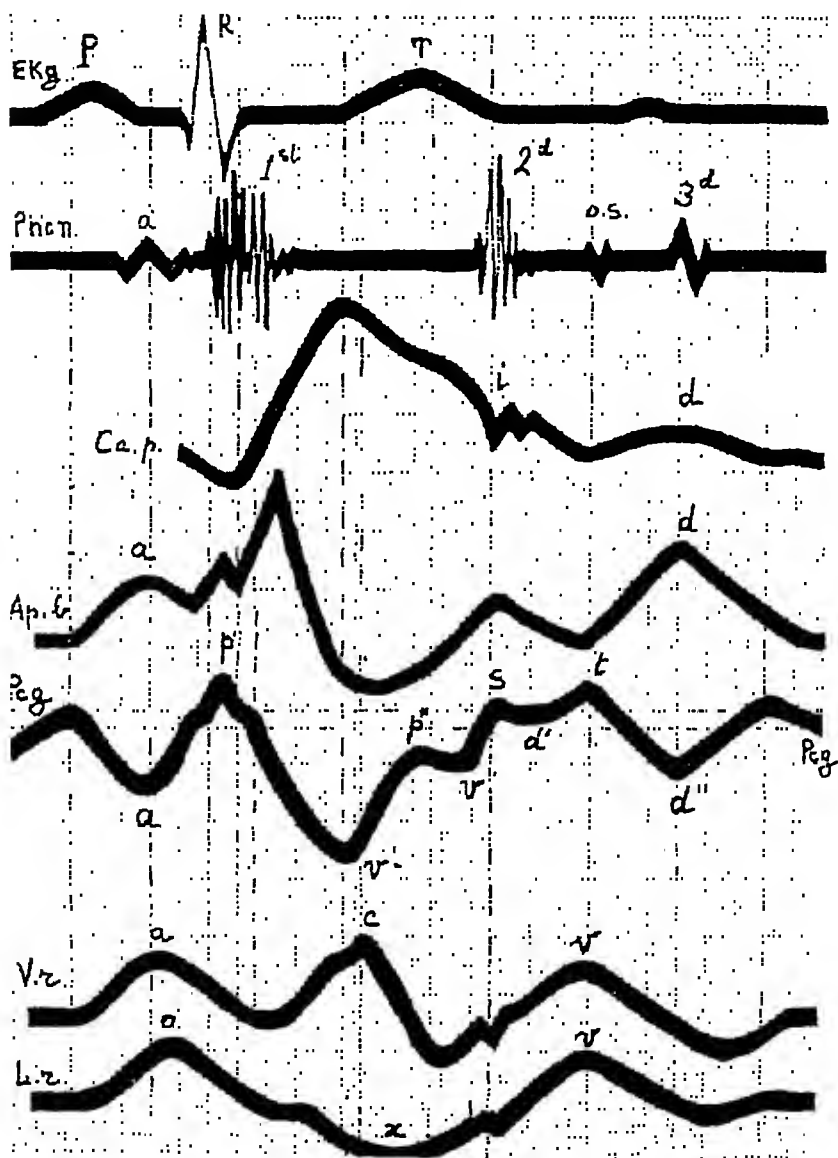


Fig. 1.—Schematic drawing of the pneumocardiogram and time relation of its waves with the waves of the different tracings. *Ekg*, electrocardiogram; *Phon.*, phonocardiogram; *Ca.p.*, carotid pulse; *Ap.b.*, apex beat; *Pcg.*, pneumocardiogram; *V.r.*, venous record on the jugular vein; *L.r.*, liver record.

waves, each with a definite connection with the phases of the cardiac action. Positive waves are also present, and bear a definite relation-

\*The electrical filter circuit which has been previously described does not remove every trace of the low-frequency components caused by respiration. Thus, some waves may be seen in a pneumocardiogram in one cycle and not in a succeeding one, because of the unlike rhythm of respiration and cardiac action. These respiratory components are more marked in children and excitable adults. Pneumocardiographic waves may be differentiated from respiratory waves because they occur in every succeeding cardiac cycle, although they may be somewhat modified in contour.

TABLE I

| COINCIDENCE                              |           |   |                 |                                       |  |   |   |  |
|--|-----------|---|-----------------|---------------------------------------|--|---|---|--|
| NAME OF WAVE                             | DIRECTION | PHASE   | EKG             | HEART SOUNDS                          | CAROTID PULSE                          | JUGULAR RECORD                            | APEX TRACING  |  |
| $a$<br>(Auricular)                       | Downward  | Presystolic   | Between P and Q | Auricular vibrations                  |  | $a$ wave                                  | $a$ wave  |  |
| $p^1$<br>(Papillary muscles contraction) | Upright   | Closure of tricuspid valve; starts ventricular systole          | With R-S        | First part of first sound             | Before rising of tracing               | Before bottom of wave between $a$ and $c$ | Slightly before notch of semilunar valves opening       |  |
| $v^1$<br>(First ventricular wave)        | Downward  | Early systolic  | Between S and T | End of first sound and after it       | With first part of carotid pulse       | With $c$ wave                             | With first part of tracing (upright then downward wave) |  |
| $p^2$<br>(Peripheral pulse)              | Upright   | Mid-systolic  | Beginning of T  | Between first and second sounds       | Immediately after apex of pulse wave   | Descending phase of $c$                   | Bottom of systolic depression                           |  |
| $r^2$<br>(Second ventricular wave)       | Downward  | Late systolic   | During T        | Before second sound                   | Before incisura                        | Bottom between $c$ and $r$                |   |  |
| $s$<br>(Semilunar valve closure)         | Upright   | Closure of aortic valves; ends ventricular systole              | End of T        | Second sound                          | Incisura                               | Notch recording second sound              | Peak of wave recording closure of semilunar valves      |  |
| $d^1$<br>(First diastolic wave)          | Downward  | Interval between semilunar valve closure and A-V valves opening | After T         | After second sound                    | During oscillations following incisura | Ascending part of $v$                     | Descending part of tracing                              |  |
| $i$<br>(Tricuspid valve opening)         | Upright   | Opening of tricuspid valve                                      |                 | Eventual opening snap of mitral valve |  | Apex of $v$ wave                          | Bottom of depression                                    |  |
| $d^2$<br>(Second diastolic wave)         | Downward  | Rapid filling of ventricles                                     |                 | Third sound                           | Dicrotic wave                          | Descending part of $r$                    | Peak of wave marking rapid filling                      |  |

ship to cardiac action. Essentially, there are only two positive waves. Positive waves are those which reach a level above the base line (Fig. 1). The junction point between some of the adjacent negative waves may become more positive and reach an amplitude above the base line.

The following description and Table I should be compared with Fig. 1, which represents the average of our normal records. Actual pneumocardiograms are reproduced in the following figures.

In describing the component waves, I have not altered the nomenclature used in 1928. There is a larger number of waves because of better recordings, so that the  $v$  wave and the  $d$  wave are now split in two, and bear the names  $v^1$  and  $v^2$ ,  $d^1$  and  $d^2$ . The initials  $a$ ,  $v$ ,  $d$ , etc., are the first letters of the terms they represent and are, therefore, easy to remember.

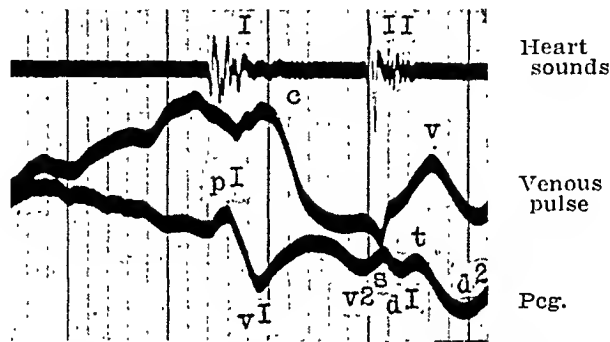


Fig. 2.—Heart sounds, pneumocardiogram, and jugular record in recumbent position. Simultaneous occurrence of the notches and of the second sound.  $v$  occurs at the same time as the  $v$  wave of the jugular record. The wave  $d^2$  slightly precedes the bottom of the depression following the  $v$  wave of the jugular record.

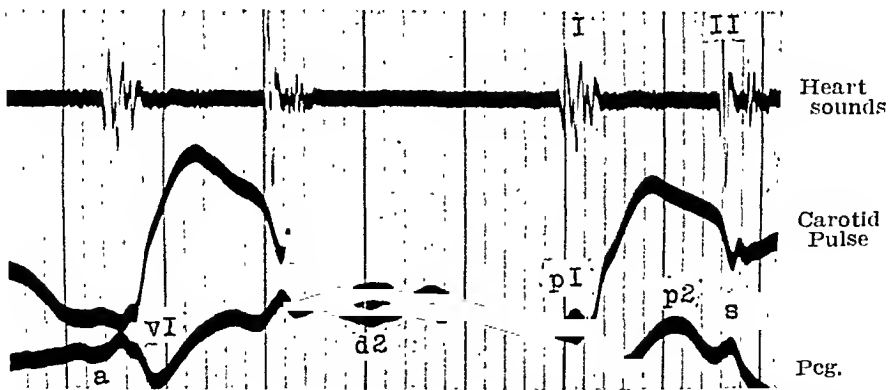


Fig. 3.—Heart sounds, carotid pulse, and pneumocardiogram in recumbent position. Time relation of  $p.v$ ,  $p^2$ , and  $v^2$  with the chief wave of the carotid pulse.

During *presystole*, the phase in which the auricles contract, there is a negative wave in the pneumocardiogram. It is designated as the  $a$  wave, or auricular wave. It is produced by stasis of blood, and often by backflow in the large veins, caused by the contraction of the right auricle. Arterial outflow plus venous stasis (or slight venous outflow) cause an inrush of air into the thorax, and therefore a depression in the pneumocardiogram (Figs. 3, 8).

*Beginning of Systole.*—Before the jugular pulsation reaches the bottom between *a* and *c* (see Figs. 1, 2), a small positive wave occurs in the pneumocardiogram. The systolic wave of the apex beat at this phase of the cycle is just beginning, and the carotid pulsation has not yet commenced (Figs. 2, 3).

A tentative explanation is as follows: At the beginning of ventricular systole the auriculoventricular valves are slightly raised in order to close the openings, then are lowered by the contraction of the papillary muscles. This movement creates a slight aspiration of blood into the right auricle, with a resulting small outflow of air from the thorax.

This notch will be called  $p^1$  (*contraction of the papillary muscles, or first positive wave*, Figs. 2, 3, 8).

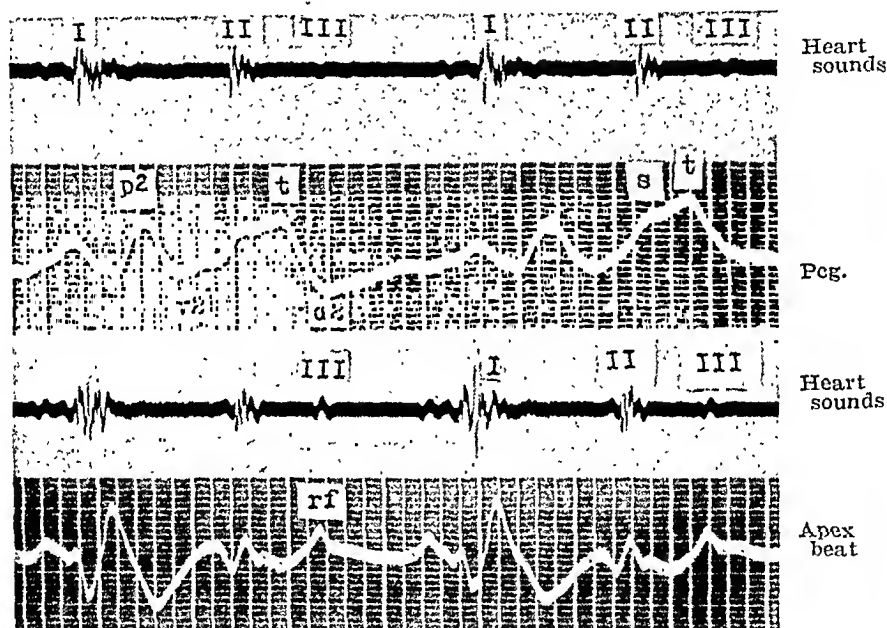


Fig. 4.—A, Record of a normal person in recumbent position. Heart sounds and pneumocardiogram. Third heart sound occurs at the same time as  $d^2$ . B, Record of the same person. Heart sounds and apex beat. The third sound is caused by rapid filling of the ventricles.

Previously, I attributed this small notch to the pulsation of the pulmonary vessels, but this explanation has been shown to be incorrect by experimental researches on dogs. When large openings are made in the dog thorax, the waves due to the movements of the heart disappear. Only small vibrations caused by the close contact of the heart and the mediastinal lobe are present. However, a new positive wave appears during the *second half* of systole which is due to the pulsation of the pulmonary vessels (Fig. 5).

*First Half of Systole.*—The blood leaves the thorax through the branches of the aortic arch and the abdominal aorta. At the same time, the venous blood either moves slowly toward the right auricle (lower vena cava, as seen in liver tracings), or has a short backflow (upper

vena cava—*c* wave of the jugular vein tracings). In this phase there is considerable aspiration of the air into the thorax, with a resulting depression in the pneumocardiogram. This wave, which is often the most marked of all, will be called  $v^1$  (*first ventricular wave*, Figs. 2, 3, 4, 6, 8).

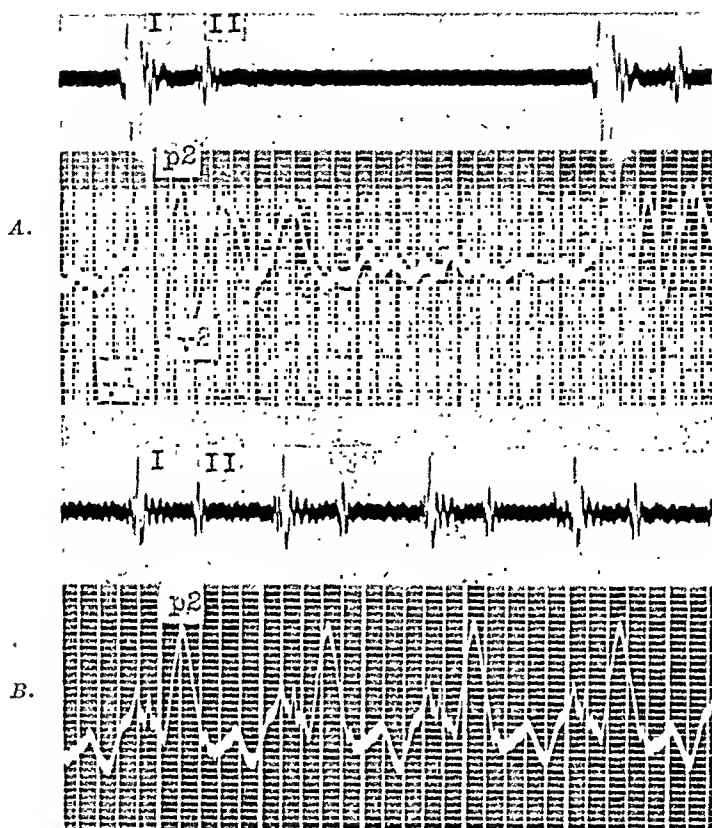


Fig. 5.—Heart sounds and pneumocardiogram of a dog under anesthesia. *A*, With closed thorax. *B*, With open thorax. The chief downward deflection is replaced by small vibrations. The systolic wave  $p^2$  is present (pulsation of the pulmonary vessels). The diastolic waves are absent when the thorax is opened.

*Midsystole*.—After the first part of systole a series of changes occurs in the dynamics of the thorax. Pronounced aspiration is exerted on the veins by the increased negative pressure within the thorax and by a lowering of the floor of the right auricle. This causes a quick flow of venous blood into the right auricle from both venae cavae, as shown by the jugular and the liver tracings. In some cases this onrushing flow may be greater than the outflowing arterial blood. Therefore, the pneumocardiogram will show an upright notch which normally does not reach the zero line, but in some cases may have a positive value.

The pulsation of the pulmonary arteries (Fig. 7)\* and that of the tracheal and nasopharyngeal vessels also contribute to the formation of

\*Theoretically, the pulsation of the pulmonary vessels should not produce any change on the pneumocardiogram, because the blood movement is intrathoracic. However, the contact between small lung arteries and alveolar air is so intimate that the following occurrence is quite probable: The decreased volume of the right ventricle will affect the venous flow to a greater extent, and the increased volume of the lungs will have greater effect on the air flow.

this wave. The name of this wave will be  $p^2$  (*peripheral pulse*, or *second positive wave*, Figs. 2, 4, 6, 8).

*Second Half of Systole.*—In this phase little blood enters the thorax, as the right auricle is nearly filled. At the same time the blood continues its outflow from the aortic arch into the peripheral vessels. Therefore, a negative wave occurs in the pneumocardiogram, as evidence of the inflow of air into the thorax. In some cases this wave is larger than  $v^1$  (see Figs. 2 and 4A). The name of this wave will be  $v^2$  (*second ventricular wave*).

*Closure of Aortic and Pulmonary Valves.*—The former phase ends abruptly with the closure of the aortic valve, which is evidenced by the presence of the aortic second sound. An upright notch occurs in the pneumocardiogram simultaneously with the second sound and with the incisura of the carotid pulse. We shall designate this wave of the pneumocardiogram by the letter  $s$  (*semilunar valve closure*, Figs. 2 and 3).

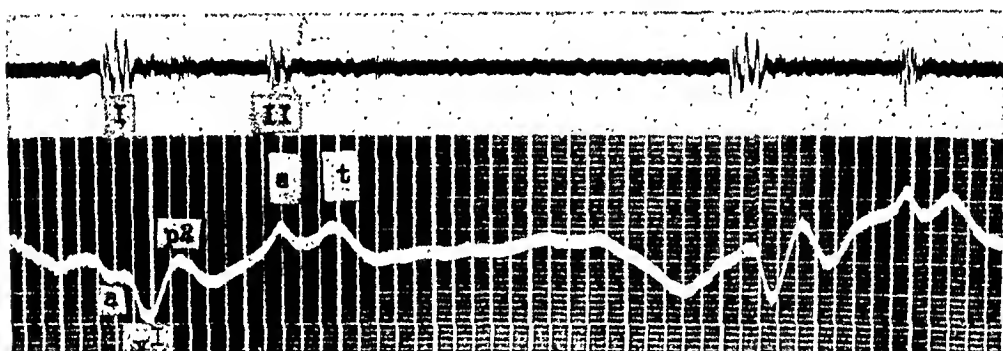


Fig. 6.—Heart sounds and pneumocardiogram in a patient with bradycardia (43 per minute).

*First Part of Diastole.*—A short time elapses between the closure of the aortic valve and the opening of the tricuspid valve. During this phase either a small downward wave or a straight line is seen in the pneumocardiogram. This wave we shall call  $d^1$  (*first diastolic wave*, see Figs. 1, 2, 8C).

*Opening of the Tricuspid Valve.*—The opening of the tricuspid valve causes a sudden onrush of blood from the venoauricular reservoir into the right ventricle. The moment of transition is indicated by a fairly clear upright notch, which may become a decidedly positive wave. Its designation will be  $t$  wave (*tricuspid valve opening*). It occurs simultaneously with the lowest point of the apex record, and with, or before, the peak of the venous pulse  $v$  wave (Figs. 1, 2, 4).

*Second Part of Diastole.*—An increased amount of blood leaves the thorax at the time of the diastolic wave in the aorta. During this phase the aortic valve is closed, but the elastic retraction of the aorta still forces blood into the periphery. Blood rushes quickly from the right auricle into the right ventricle because of the difference in pressure.

Because of a tonic adaptation of the right auricle, the amount of venous blood which enters the auricle at this time is not very large. There occurs, as a result, an inflow of air into the thorax which causes a deep negative wave in the pneumocardiogram ( $d^2$ , or second diastolic wave). It is important to mention at this time that the peak of the diastolic wave of the apex cardiogram occurs simultaneously with  $d^2$  of the pneumocardiogram. The *third heart sound*, which indicates rapid filling of the ventricles, occurs simultaneously with the point of maximum depression of  $d^2$  (Fig. 4).

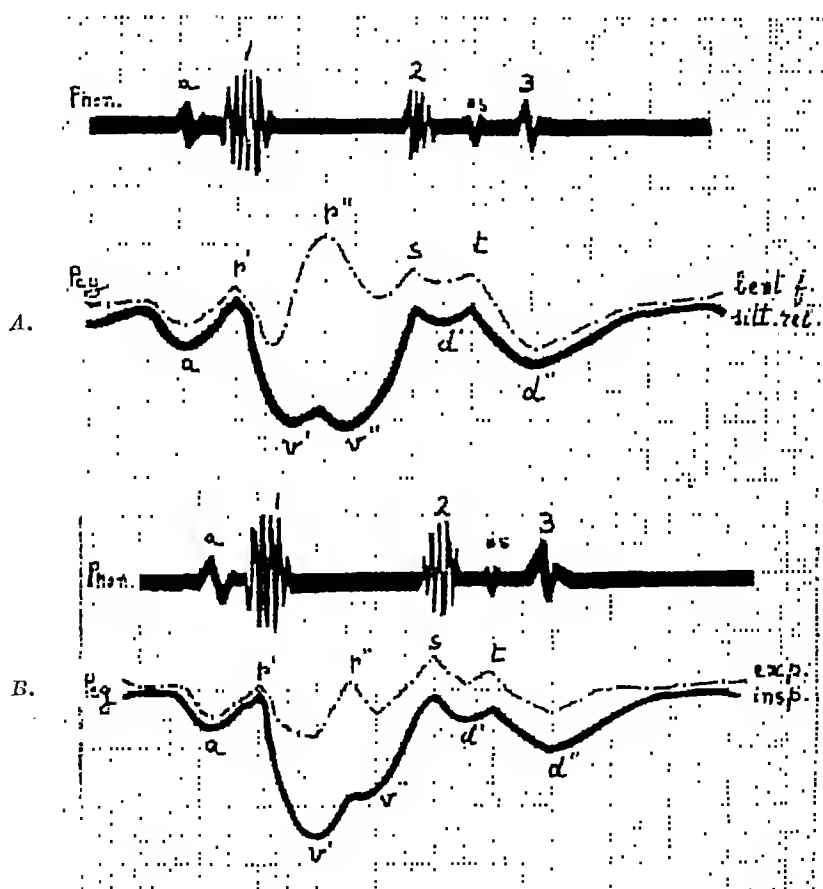


Fig. 7.—Schematic drawing of the changes due to respiration and position. A. ———, sitting relaxed; - - - - -, bent forward. B. ———, inspiration; - - - - -, expiration.

A number of additional diastolic waves may occur in the pneumocardiogram when diastole is prolonged; they are the result of changes of pressure in the thorax. Additional negative waves in the pneumocardiogram may be called  $d^3$ ,  $d^4$ , etc. (*late diastolic waves*).

#### PHYSIOLOGIC VARIATIONS IN THE PNEUMOCARDIOGRAM

*Respiratory Changes.*—By placing the hand on the abdomen of the patient, and indicating each abdominal depression on the record with the lead marker during each expiration, it is possible to distinguish between the two phases of respiration. During the first portion of

*inspiration*, normal persons show deeper waves in the pneumocardiogram than during other phases. However, the clarity of the record is at times not perfect during this phase, and two waves may combine as a single wave. The *a* wave is deep and broad; *p*<sup>2</sup> is smaller and of a short duration. *V*<sup>1</sup> and *v*<sup>2</sup> show a tendency to form a single, negative, systolic wave (Fig. 7).

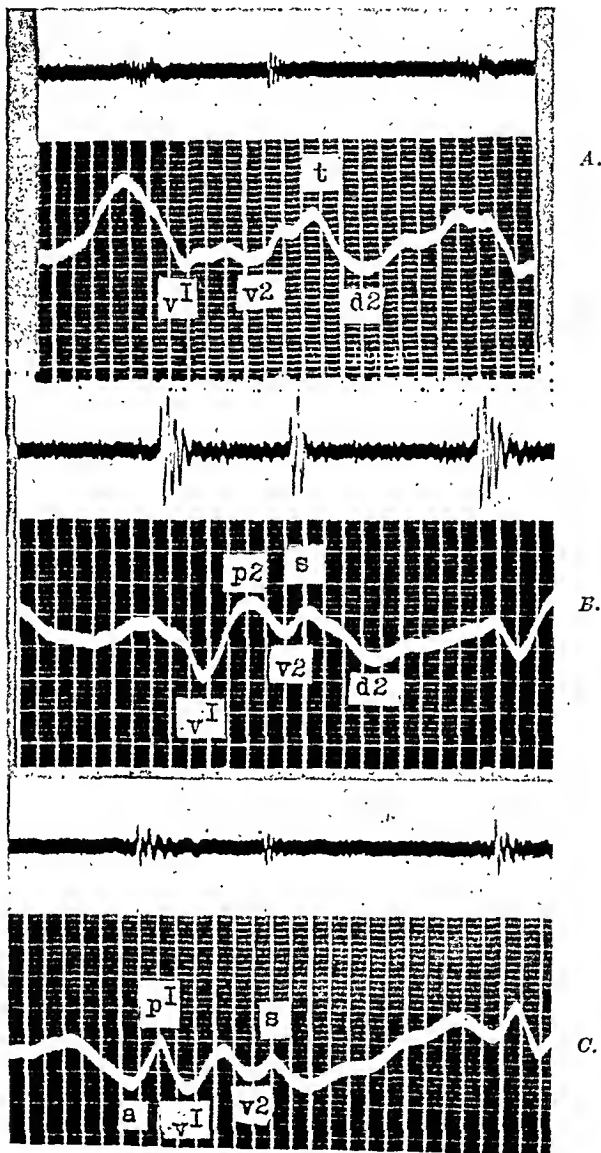


Fig. 8.—Changes in heart sounds and pneumocardiogram in different positions (normal person). Same phase of respiration. A, recumbent; B, sitting bent forward; C, standing.

During *expiration* normal persons usually show smaller waves. This is particularly true in the second half of the phase. *P*<sup>1</sup> is usually clearly defined and sharp, and *p*<sup>2</sup> is tall and broad, with a definite positivity. *T* possesses a low amplitude, but *s* is taller and often well defined (Fig. 7B).



*Inspiratory and Expiratory Standstill.*—The above described technique eliminates the necessity of requesting the patient to hold his breath in an extreme inspiratory or expiratory position, which may introduce individual variations and abnormal pressure conditions. A study was made of these extreme phases in order to compare the new technique with that used by previous observers. From a practical standpoint it has been found that the degree of inspiration or expiration is a variable quantity which depends upon the training and cooperation of the patient. There was no fundamental difference in timing or in the polarity of the waves between the changes produced in the pneumocardiogram by normal physiologic respiratory phases and those resulting from an artificial pause in the extreme positions of the thorax.

*Changes Due to Position.*—The best results are obtained in either a sitting position or a semirecumbent position, with the patient completely relaxed. Other positions, such as supine, sitting erect, sitting bent forward, or standing, may produce many important changes in the pneumocardiogram. Many of these changes were studied by Holzlöhner, and were explained by him as the result of an altered venous flow caused by modified tension of the venous wall. Figs. 7 and 8 indicate some of the changes brought about by different positions. In general, the difference between the sitting and semirecumbent positions is unimportant. Relaxation of all muscles is necessary in order to avoid error.

*Bradycardia and Tachycardia.*—Because of the shortness of diastole, persons with tachycardia often show a partial or total fusion of  $d^2$  and  $a$ . The amplitude of the wave between  $s$  and  $t$  is often increased.

These variations may be explained by similar changes in diastolic venous inflow and by the abrupt systolic collapse of the veins.

In bradycardia, on the other hand, the waves are typical, and a number of additional waves, such as  $d^3$  and  $d^4$ , may occur during diastole.

#### THE PRACTICAL VALUE OF THE PNEUMOCARDIOGRAM

The pneumocardiogram has a number of important clinical applications. Routine clinical phonocardiography has indicated to me that at times it is rather difficult to explain the nature of one or more extra sounds which may occur in the cardiac cycle. The phlebogram is at times unreliable for this purpose. For instance, the use of the venous pulse  $v$  wave for the differentiation between an *opening snap* of the mitral valve and the *third sound* is sometimes erroneous. This has been observed by Taquini, Walsh, and Massell<sup>39</sup> in cases of mitral regurgitation, in which the isometric relaxation phase may be shortened. The result is that the *third heart sound* occurs approximately where the *opening snap* should be. I have observed a number of normal persons whose *third sound* almost coincided with the peak of the  $v$  wave.

The apex eardiogram, as indicated by Taquini, et al., is more reliable. However, the apex eardiogram is not always recordable. The pneumoeardiogram, for this differentiation, is always recordable with the new technique. In taking a large number of pneumoeardiograms with this new technique, I have observed that there is a constant time relationship between four waves of the pneumoeardiogram and four phases of the heart cycle, namely:

- $p^1$  = closure of the tricuspid valve
- $s$  = closure of the aortic valve
- $t$  = opening of the tricuspid valve
- $d^2$  = rapid inflow into the ventricles

Three of these pneumoeardiographic waves coincide with definite acoustic phenomena which are, or may be, present in normal persons and/or in pathologic conditions, namely:

- $s$  = second heart sound
- $t$  = "opening snap" of the mitral valve
- $d^2$  = third heart sound

The relationship between pneumoeardiographic and phonocardiographic waves is constant, although the contour of these waves may vary from person to person. Future experience should indicate whether the pneumoeardiogram will also have diagnostic value with respect to asynchronous valve closure of the two ventricles.

Study of the pneumoeardiogram in valvular defects and in arrhythmias has been carried out on a fairly large scale by previous authors and by me. However, in my opinion, the development of superior apparatus which allows the employment of this new pneumoeardiographic technique warrants a repetition of the study in order to establish a more exact basis for the variations brought about by various cardiac abnormalities. It is conceivable that some of the typical changes that occur in the pneumoeardiogram may assume a diagnostic value.

#### SUMMARY

1. There are rhythmic pulsations in the respiratory air passages which are caused by the heart beat.
2. A new and easily applied technique is described for the graphic registration of the cardiac waves during every phase of normal respiration. I suggest calling this tracing the internal *pneumocardiogram*, a name which is self-explanatory.
3. Pneumocardiograms were obtained on normal persons, and the component waves are herein analyzed.
4. As a result of previous and recent experiments (intrathoracic pressure records in man, opening of the thorax in animals), the possibility that the apex beat causes these waves is eliminated.

5. Multiple waves are produced in the pneumocardiogram by the difference between venous inflow to, and arterial outflow from, the thorax.

6. Five negative and four positive waves are described.

7. The coincidence between three of the positive waves and valvular movements is demonstrated. The coincidence of one of the negative waves with rapid filling of the ventricles is also established.

8. Changes brought about by different positions and by respiratory phases have been studied.

9. The importance of the pneumocardiogram in clinical diagnosis has been indicated.

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## ELECTROCARDIOGRAPHIC CHANGES IN BRONCHIAL ASTHMA AND THEIR SIGNIFICANCE

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IN A recent communication by one of us (J.H.),<sup>1</sup> clinical and pathologic evidence was presented in support of the concept that the electrocardiographic abnormalities associated with asthmatic attacks in certain cases of bronchial asthma were manifestations of an underlying hyperergic vascular disease. This work suggested study, with special reference to the electrocardiograms, of an additional group of fifty patients with bronchial asthma who were admitted to the hospital during the past five years. Persons with evidence of organic heart disease, hypertension, generalized arteriosclerosis, or other associated illnesses were excluded from this investigation.

Although electrocardiographic abnormalities in bronchial asthma have been described by various authors, no attempt has been made to interpret the mechanism involved in their evolution. Kahn<sup>2</sup> called attention to the frequency of right axis deviation, and noted the presence of enlarged P waves in four of ten cases in which there was right axis deviation. Unger,<sup>3</sup> in reviewing seventy-four cases, also found right axis deviation which was well developed in four cases and suggestive in thirty-five. Crip,<sup>4</sup> in a study of eight patients during acute paroxysms of asthma, observed that six had normal electrocardiograms, one had abnormalities of conduction, characterized by an increase in the P-R interval, and another had extrasystoles. Colton and Ziskin<sup>5</sup> reported delayed conduction, arborization block, and negative T waves in eleven, or 20 per cent, of fifty cases of bronchial asthma. They regarded these changes as evidence of myocardial involvement which appeared only in those patients who had had asthma ten years or longer. In one case they observed T-wave inversion which disappeared with the subsidence of the paroxysmal attacks.

Of the fifty patients investigated in this study, twenty presented the following electrocardiographic changes, exclusive of sinus tachycardia: (1) prominent P waves, (2) QRS disturbances, (3) RS-T transition changes, and (4) T-wave alterations (Table I).

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## SUMMARY OF THE CLINICAL OBSERVATIONS

A review of the constitutional background of the twenty patients indicated the presence of a personal or family history of allergy in only five. Sinus infection proved to be the major exciting agent in eighteen of the cases, and, in eight of these, food and inhalant sensitivity, including pollen, was likewise demonstrable. The provocative factors in the remaining two cases were not ascertained. The duration of the asthma varied from eight months to thirty-four years. The youngest patient in the series was 18, and the oldest, 60 years of age (Table I).

*Pulmonary Lesions.*—Examination of the lungs disclosed the sonorous râles which are characteristic of bronchial asthma in all of the twenty cases. In the majority of the cases, in spite of the dyspnea, there was no severe cyanosis. Roentgenologic examination of the lungs during acute paroxysms revealed pulmonary infiltration in six cases (Cases 1, 8, 9, 13, 14, and 16). These lesions, also diagnosed as "interstitial pneumonitis" by the roentgenologist, were found to be reversible in character in five of the six patients who could be followed. With the termination of the acute asthmatic attacks, resolution of the pulmonary infiltrations occurred. The eosinophile count in these cases ranged from 5 to 84 per cent.

In the remaining fourteen cases, roentgenograms revealed emphysema in two, lung cysts in two, and nothing abnormal in the other ten. The eosinophile count in this group was between 1 and 4 per cent.

*Cardiac Manifestations.*—The hearts of the patients under investigation were negative on auscultation, but tachycardia, ranging between 100 and 130 beats per minute, occurred during asthmatic attacks. Moderate enlargement of the left and right ventricles was found in one case (Case 10). This was confirmed by roentgenologic examination, which disclosed enlargement of the transverse diameter. The blood pressure in each case was normal. A maximum systolic pressure of as much as 140 was present in only four of the twenty cases.

The electrocardiographic abnormalities consisted of high P waves alone in six cases, and high P waves with QRS and T-wave deviations in nine others. In the remaining five cases the alterations were confined to the QRS and T waves only. The QRS changes included slurring, notching, and low voltage, and the T waves were low, isoelectric, or inverted.

In nine of the twenty cases the electrocardiographic abnormalities disappeared with the termination of the asthmatic paroxysm, whereas in five cases the changes persisted.

In the group with reversible electrocardiographic changes, two patients (Cases 1 and 2, Table I), showed alterations in the P wave only, four (Cases 7, 8, 9, and 13, Table I) had changes in the P waves, QRS complexes, and T waves, and three (Cases 16, 17, and 18, Table I)

TABLE I

| CASE           | PA-TIENT | SEX | AGE (YEARS) | FAMILY HISTORY OF ALLERGY       | ETIOLOGY  | DURATION OF ASTHMA | PHYSICAL EXAMINATION OF LUNGS                                | ROENTGENOGRAM OF CHEST  | BLOOD EOSINOPHILES | PHYSICAL EXAMINATION OF HEART | BLOOD PRESSURE | ELECTROCARDIOGRAPHIC OBSERVATIONS  |
|----------------|----------|-----|-------------|---------------------------------|---|--------------------|--|---|--------------------|-------------------------------|----------------|--|
| <i>Group 1</i> |          |     |             |                                 |   |                    |  |   |                    |                               |                |  |
| 1              | L. Z.    | M   | 30          | Asthma in maternal grand-mother | Chronic sinusitis. Sensitivity to foods and inhalants       | 5 years            | Occasional sibilant râles throughout both lungs              | Interstitial infiltration, both lower lobes. Return to normal | 5%                 | Negative                      | 115/75         | 2/3/39. High wide P waves. Return to normal with subsidence of asthma  |
| 2              | R. A.    | F   | 18          | Paternal uncle has hay fever    | Chronic sinusitis. Sensitivity to pollens and foods         | 6 months           | Sibilant and sonorous râles throughout                       | Negative  | 9%                 | Negative                      | 125/70         | 3/21/39. Sinus tachycardia, rate 130. High P waves. Right axis deviation. Return to normal with subsidence of asthma |
| 3              | R. F.    | M   | 42          | Negative                        | Chronic sinusitis. Sensitivity to foods, pollens, and molds | 13 years           | Sibilant and sonorous râles throughout. Prolonged expiration | Large cyst at left base                                       | 3%                 | Negative                      | 140/90         | 8/23/39. Sinus tachycardia, rate 110. High P waves. Unchanged after 8 months. 4/3/40                                 |
| 4              | P. M.    | M   | 24          | Negative                        | Chronic sinusitis. Sensitivity to foods                     | 2 years            | Sibilant and sonorous râles throughout                       | Negative  | 8%                 | Negative                      | 100/80         | 1/24/39. High P waves in Leads II and III. No follow-up  |
| 5              | S. G.    | F   | 39          | Negative                        | Chronic sinusitis. Sensitivity to foods                     | 34 years           | Diminution of breath sounds, râles at bases                  | Infiltration about lipiodol deposits in lower lobes           | 3%                 | Negative                      | 134/80         | 3/28/39. Sinus tachycardia, rate 130. High P waves. No follow-up   |

|         |       |   |    |                                      |   |          |  |   |           |          |        |  |
|---------|-------|---|----|--------------------------------------|---|----------|--|---|-----------|----------|--------|--|
| 6       | J. S. | M | 51 | Father had asthma; sister, urticaria | Chronic sinusitis. Sensitivity to foods and inhalants | 30 years | Wheezing. Sibilant and sonorous râles throughout | Moderate pulmonary emphysema  | 0         | Negative | 140/82 | 4/7/39. Sinus tachycardia, rate 105. High P waves. No follow-up  |
| Group 2 |       |   |    |                                      |   |          |  |   |           |          |        |  |
| 7       | R. K. | M | 20 | Negative                             | Sensitivity to pollen and tobacco                     | 8 months | Sibilant and sonorous râles throughout. Wheezing | Negative  | 7%        | Negative | 110/80 | 3/26/40. Sinus tachycardia. P waves high. QRS 1, 2, and 3 low. 5 minutes after ad renalin P wave small and inverted. Slight elevation of QRS 1 and 2. Slowing of heart rate  |
| 8       | P. D. | M | 41 | Negative                             | Chronic sinusitis                                     | 3 years  | Sibilant and sonorous râles. Wheezing            | Interstitial infiltration. Return to normal   | 30 to 84% | Negative | 125/80 | 8/1/35. Right ventricular preponderance. P waves high, QRS slurred. T <sub>2</sub> and T <sub>3</sub> inverted. 9/6/35. T <sub>2</sub> isoelectric. 11/16/35. T <sub>1</sub> higher, T <sub>3</sub> upright, EKG returning to normal                                   |
| 9       | F. H. | F | 21 | Negative                             | Chronic purulent sinusitis                            | 5 years  | Sibilant and sonorous râles throughout. Wheezing | Five recurrent attacks of interstitial pulmonary infiltration, migrating in various lobes of lung during a period of 4 years, returning to normal each time | 35 to 50% | Negative | 120/80 | 4/11/39. P waves high in Leads II and III. T <sub>2</sub> and T <sub>3</sub> low. 6/2/39. Leads I and II normal, Q <sub>2</sub> present. During an attack of polyarthritis, 9/10/40, sinus tachycardia, T waves low to semi-inverted. 11/1/40, T wave becoming upright |



TABLE I—CONT'D

| CASE | PATIENT | SEX | AGE (YEARS) | FAMILY HISTORY OF ALLERGY | ETIOLOGY  | DURATION OF ASTHMA | PHYSICAL EXAMINATION OF LUNGS   | ROENTGENOGRAM OF CHEST   | BLOOD EOSINOPHILES | PHYSICAL EXAMINATION OF HEART   | BLOOD PRES-SURE | ELECTROCARDIOGRAPHIC OBSERVATIONS  |
|------|---------|-----|-------------|---------------------------|---|--------------------|---|--------------------------|--------------------|---|-----------------|--|
| 10   | G. R.   | F   | 39          | Son has asthma            | Chronic sinusitis. Sensitivity to pollens and foods | 2 years            | Sibilant and sonorous râles. Wheezing                                       | Negative                 | 16%                | Enlargement of the right and left ventricles confirmed by x-ray. No adventitious sounds | 110/68          | 5/23/40. P waves high. QRS 1, 2, and 3, small and slurred. T <sub>2</sub> diaphasic, T <sub>3</sub> inverted. Asthma and EKG changes persist.  |
| 11   | S. B.   | F   | 43          | Father had asthma         | Chronic sinusitis                                   | 4 years            | Sibilant and sonorous râles throughout. Hyperresonant, prolonged expiration | Negative                 | 0                  | Negative  | 100/80          | 5/12/39. P waves high. T <sub>2</sub> low, T <sub>3</sub> inverted. RS-T <sub>2</sub> , RS-T <sub>3</sub> depressed. 7/20/39, six weeks later, P waves high. T waves and RS-T normal |
| 12   | R. M.   | F   | 38          | Negative                  | Chronic sinusitis                                   | 2 years            | Sibilant and sonorous râles throughout. Wheezing                            | Cyst in right upper lobe | 2%                 | Negative  | 120/70          | 2/6/39. Sinus tachycardia, rate 105. P waves high. QRS low. Tendency to R.A.D. Asthma and EKG changes persist  |

|    |       |   |    |          |   |          |  |  |     |          |        |   |
|----|-------|---|----|----------|---|----------|--|--|-----|----------|--------|---|
| 13 | E. C. | F | 42 | Negative | Chronic sinusitis. Sensitivity to pollens and inhalants | 28 years | Sibilant and sonorous râles throughout                       | Interstitial infiltration, right upper and lower lobes. Return to normal | 16% | Negative | 105/80 | 3/25/41. Sinus tachycardia, rate 120. R-T segments depressed in Leads II and III. T <sub>2</sub> and T <sub>3</sub> diphasic. Right axis deviation. 4/11/41. Return to normal |
| 14 | G. S. | F | 37 | Negative | Chronic sinusitis                                       | 9 years  | Sibilant and sonorous râles throughout                       | Interstitial infiltration of right lower lobe                            | 9%  | Negative | 128/85 | 12/27/38. P wave high, QRS low. T <sub>1</sub> , T <sub>2</sub> , and T <sub>3</sub> low. No follow-up  |
| 15 | S. G. | M | 48 | Negative | Chronic sinusitis                                       | 15 years | Emphysema-tous chest. Sibilant and sonorous râles throughout | Emphysema. Large blebs in both lungs                                     | 1%  | Negative | 120/80 | 6/17/36. Sinus tachycardia, rate 125. P waves high. Tendency to R.A.D. QRS low. No follow-up  |

## Group 3

|    |       |   |    |                                 |                   |          |   |   |           |          |        |   |
|----|-------|---|----|---------------------------------|-------------------|----------|---|---|-----------|----------|--------|---|
| 16 | L. G. | F | 48 | Mother had asthma and hay fever | Chronic sinusitis | 2 years  | Wheezing. Sibilant and sonorous râles throughout                                  | Acute interstitial infiltration in right upper lobe. Return to normal | 26 to 47% | Negative | 105/70 | 11/4/38. T <sub>1</sub> semi-inverted. T <sub>2</sub> and T <sub>3</sub> inverted. Two weeks later, when asthmatic attack had subsided, EKG became normal   |
| 17 | F. R. | F | 60 | Negative                        | Chronic sinusitis | 11 years | Wheezing, prolonged expiration. Sibilant and sonorous râles throughout. Emphysema | Heart enlarged to left  | 4 to 12%  | Negative | 120/74 | 7/28/39. Left axis deviation. QRS slurred, of low amplitude, in Lead II. R-T segment depressed in Lead I, elevated in Lead III; T <sub>1</sub> and T <sub>3</sub> low. Nine days later, when asthma subsided, EKG became normal |

TABLE I—CONT'D

| CASE | PATIENT | SEX | AGE (YEARS) | FAMILY HISTORY OF ALLERGY | ETIOLOGY  | DURATION OF ASTHMA | PHYSICAL EXAMINATION OF LUNGS                                      | ROENTGENOGRAM OF CHEST | BLOOD EOSINOPHILES | PHYSICAL EXAMINATION OF HEART | BLOOD PRESSURE | ELECTROCARDIOGRAPHIC OBSERVATIONS   |
|------|---------|-----|-------------|---------------------------|---|--------------------|--|------------------------|--------------------|-------------------------------|----------------|---|
| 18   | A. H.   | F   | 56          | Negative                  | Chronic sinusitis. Sensitivity to foods and inhalants | 3 years            | Sibilant and sonorous râles throughout                             | Negative               | 4 to 8%            | Negative                      | 149/90         | 3/11/39. RS-T <sub>2</sub> depressed, T <sub>2</sub> diphasic. T <sub>3</sub> isoelectric. When asthma had subsided, EKG became normal  |
| 19   | D. C.   | F   | 38          | Negative                  | Undetermined  | 11 years           | Wheezing. Sibilant and sonorous râles throughout                   | Negative               | 2%                 | Negative                      | 140/80         | 6/29/36. T <sub>1</sub> inverted. EKG taken between 2 asthmatic attacks. 9/8/36. Patient died in status asthmaticus   |
| 20   | G. E.   | F   | 48          | Negative                  | Chronic sinusitis. Sensitivity to foods               | 3 years            | Wheezing, prolonged expiration, crepitating râles throughout lungs | Emphysema. Lung cyst   | 4%                 | Negative                      | 130/80         | 12/1/39. QRS low in all leads. T <sub>2</sub> low. T <sub>3</sub> inverted. 4/26/40. T <sub>1</sub> , T <sub>2</sub> and T <sub>3</sub> isoelectric. Moderately severe asthma present |

presented disturbances limited to the QRS and T waves. Despite the fact that the last three patients were the oldest in the series (45, 56, and 60 years of age, respectively), the myocardial disturbances responsible for their electrocardiographic abnormalities were reversible.

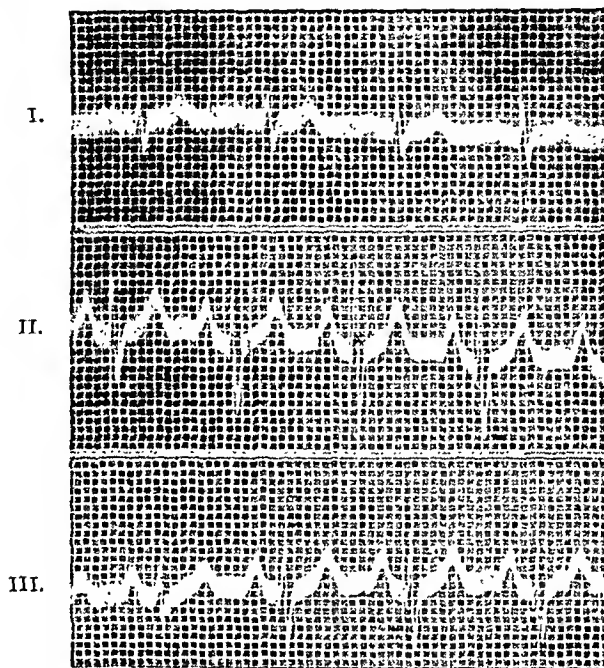


Fig. 1.—Case 4, Group 1. P. M., male, aged 24 years. Record taken Jan. 24, 1939, shows enlarged P waves in Leads II and III.

One of the five patients (Case 3) with irreversible changes showed persistent enlargement of the P waves only. This man had had asthma for thirteen years, together with pulmonary emphysema and a lung cyst. The other four patients presented changes in the P, QRS, and T waves. Of these, one patient (Case 10, Table I), aged 39, had enlargement of the right and left sides of the heart without demonstrable emphysema; a second (Case 11) had slight enlargement of the right side of the heart and moderate emphysema disclosed at autopsy; the third (Case 12) had evidence of right ventricular preponderance with marked emphysema and a lung cyst; and the fourth (Case 20), of group three, showed deviations limited to the QRS complexes and T waves, associated with continuous asthma, emphysema, and lung cyst.

The remaining six patients could not be classified as to reversibility or irreversibility of the changes because of inadequate follow-up studies. Of these, three (Cases 4, 5, and 6) showed high P waves only; two (Cases 14 and 15) presented changes in the P, QRS, and T waves; and one (Case 19) had deviations in the T waves only.

It is to be noted that, of the nine patients with reversible electrocardiographic changes, five had intercurrent, interstitial, pulmonary infiltrations. The latter, together with the electrocardiographic changes,

disappeared with the termination of the asthmatic seizures, but not simultaneously with every attack. Thus, in two (Cases 8 and 9 of Group 2), the electrocardiographic changes persisted while lesions in other tissues were appearing, although the asthma and pulmonary infiltrations had disappeared. The new developments in Case 8 consisted of polyneuritis and eosinophilic peritonitis. In Case 9 they were acute pericarditis on one occasion, and polyarthrititis associated with a maculopapular erythematous eruption which persisted for three weeks, on another. With the termination of these various complications, the electrocardiograms returned to normal in both cases. Abnormal electrocardiograms during asthma-free intervals were also observed in Case 10. In this case no pulmonary lesions were observed during asthmatic attacks.

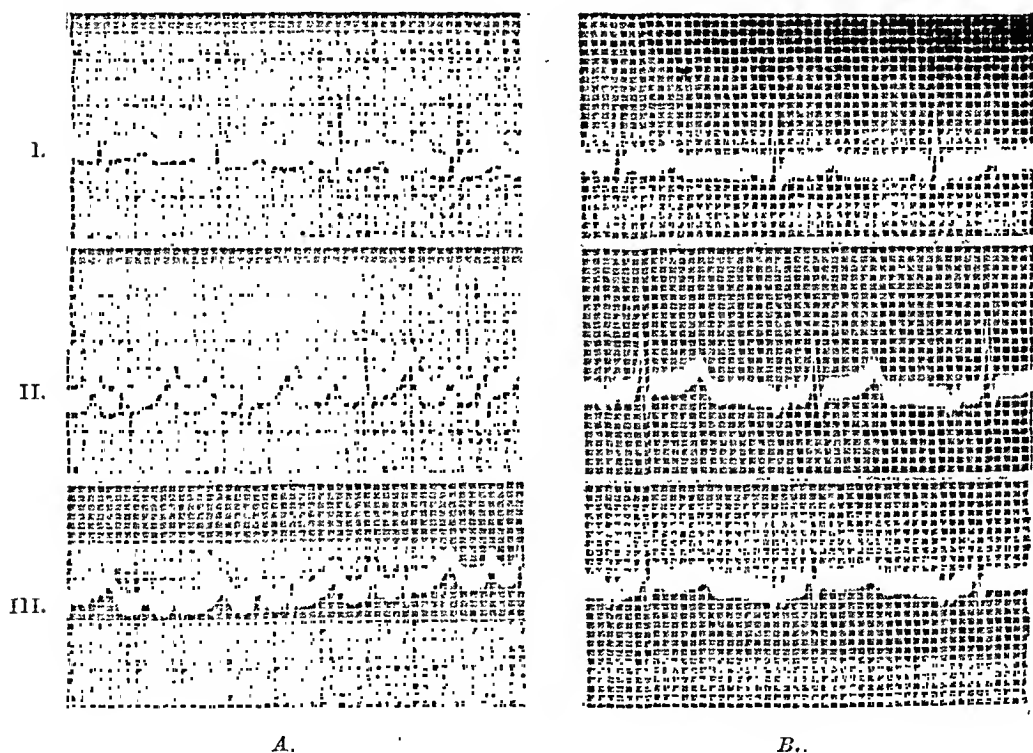


Fig. 2.—Case 7, Group 2. R. K., male, aged 20 years. A, record taken before administration of adrenalin, shows sinus tachycardia, high P waves, and low QRS. B, record taken five minutes after administration of adrenalin, shows slowing of rate, change in P waves, and higher QRS.

Studies of the arterial oxygen content by Dr. E. Somkin and Dr. A. Weiss in three of the cases (Cases 10 and 13 of Group 2, and Case 20 of Group 3) during the asthmatic attacks disclosed the following:

Patient 10, with irreversible electrocardiographic changes, showed an oxygen content of 18.65 volumes per cent and an oxygen capacity of 18.81 volumes per cent. The saturation was 99 per cent. Patient 13, who presented reversible electrocardiographic changes, showed an arterial oxygen capacity before an asthmatic attack, when her electrocardiogram was normal, of 20 volumes per cent and an oxygen content

of 18.23 volumes per cent, which gives 90 per cent saturation. During an attack she had an arterial oxygen capacity of 19.0 volumes per cent and an oxygen content of 17.0 volumes per cent, which also gives 90 per cent saturation.

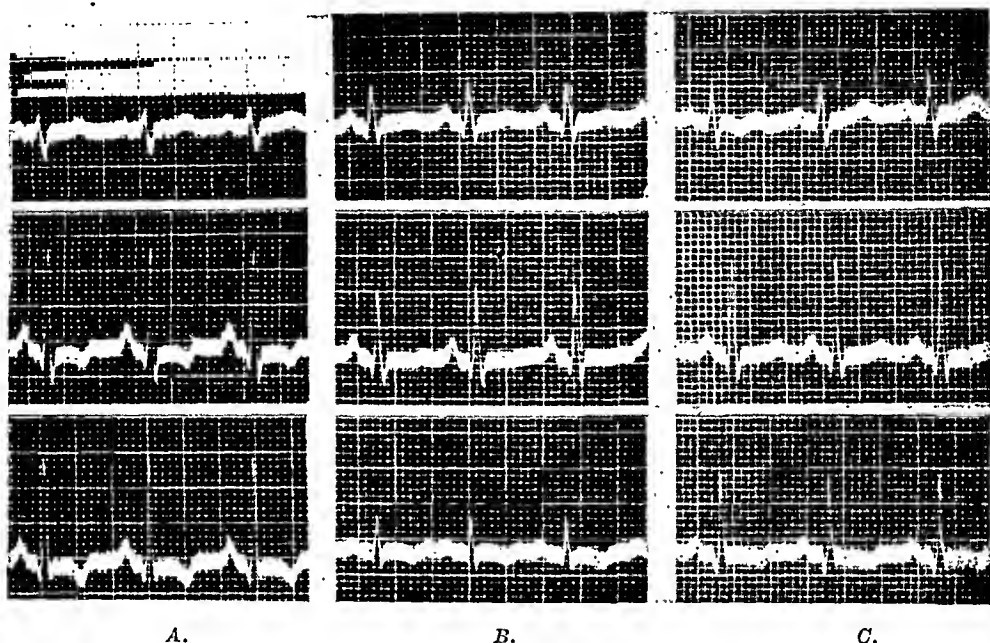


Fig. 3.—Case 8, Group 2. P. D., male, aged 41 years. *A*, record taken Aug. 1, 1935, shows tendency to R.A.D., high P waves, slurred QRS, and inverted  $T_2$  and  $T_3$ . *B*, record taken Sept. 6, 1935, shows  $T_2$  isoelectric. *C*, record taken Nov. 16, 1935, shows  $T_1$  higher and  $T_2$  upright.

Patient 20, who had chronic emphysema and a lung cyst, with irreversible electrocardiographic changes and cyanosis, showed an oxygen capacity of 22 volumes per cent and an oxygen content of 18.6 volumes per cent, indicating 84 per cent saturation.

No pertinent abnormalities referable to any other tissues were present in these cases, with the exception of nodular erythematous patches of the skin in Case 9 and reddish nodules in the conjunctivae in Case 10. Biopsy of the skin lesion in Case 9 disclosed perivascular eosinophilic infiltration, and the conjunctival nodules showed "collagen necrosis with an epithelioid giant cell reaction and marked infiltration with eosinophiles."

#### DISCUSSION

In evaluating the mechanism responsible for the various electrocardiographic changes, we considered (1) the effect of anoxemia, (2) the role of epinephrine, (3) positional changes of the heart, and (4) allergic responses in the lungs and heart.

1. *Anoxemia*.—Induced anoxemia in both experimental animals and man has resulted in prolongation of the P-R interval, alterations of the RS-T segment, and T-wave changes.<sup>6-11</sup> According to Tigges,<sup>10</sup> normal persons begin to show electrocardiographic changes at a stage

when signs of disturbances of consciousness present themselves. Levy, Barach, and Bruenn,<sup>12</sup> in a study of oxygen want in cases with cardiac pain, investigated one subject with a normal heart and noted slight flattening of the T waves in Leads I and II and a less deeply inverted T wave in Lead IV, after the inhalation of a 12 per cent oxygen mixture for twenty minutes. There was no effect on the R-T or S-T segments. The arterial oxygen saturation in this subject at the end of the experiment was 67.8 per cent. It would seem from such observations that in persons with normal hearts the oxygen want must be fairly severe before electrocardiographic changes begin to appear. The hearts of the patients studied were, with one exception, free of organic involvement.

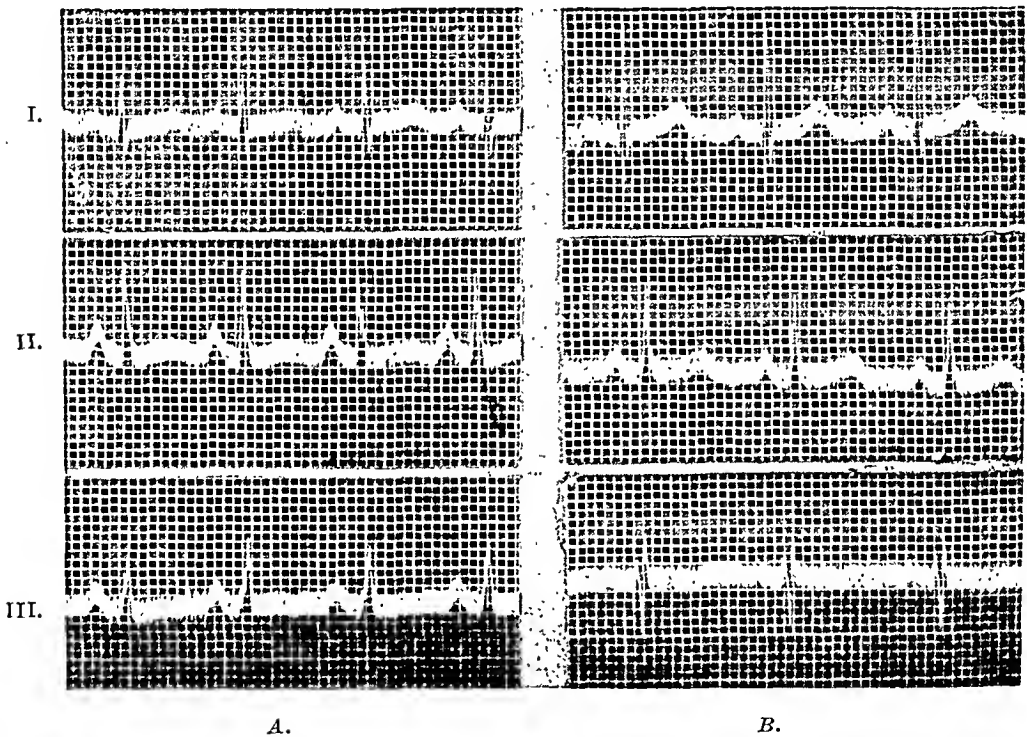


Fig. 4.—Case 9, Group 2. F. H., female, aged 23 years. A, record taken April 11, 1939, shows sinus tachycardia (rate 130), P wave high in Leads II and III, and T<sub>2</sub> and T<sub>3</sub> low. B, record taken June 2, 1939, shows normal Leads I and II and presence of Q<sub>3</sub>.

The question of anoxemia in bronchial asthma has been dealt with by a number of investigators. In summarizing the observations up to 1929, Walzer,<sup>13</sup> quoting Wittkower, stated that, in the majority of cases, the oxygen saturation of the arterial blood is low, or at the lower threshold of normal, whereas the alveolar CO<sub>2</sub>, the CO<sub>2</sub> combining power, and the pH of the blood are normal. This would indicate that there is no marked state of anoxemia in the uncomplicated cases of bronchial asthma. Meakins and Davies<sup>14</sup> found that, in certain types of asthma, accompanied by bronchitis, emphysema, and marked cyanosis, there was a varying degree of oxygen desaturation. There was no record of any electrocardiographic abnormalities in the cases which

they studied, and they concluded that the lowering of the arterial blood oxygen is directly proportional to the chronicity of the lesion and the extent of the emphysema and bronchitis. Their inability to increase the oxygen saturation of the blood to normal in certain instances by oxygen inhalation caused them to speculate concerning the possibility of underlying vascular involvement in these cases.

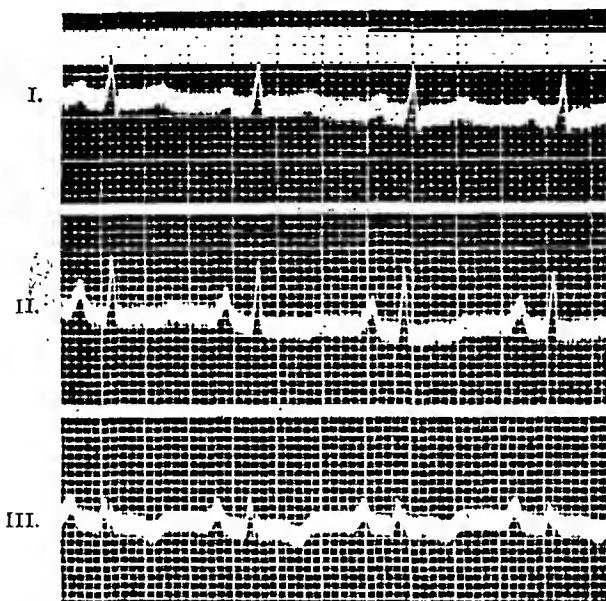


Fig. 5.—Case 10, Group 2. G. R., female, aged 39 years. Record taken May 23, 1940, shows P waves high, QRS low and slurred,  $T_2$  diphasic, and  $T_3$  inverted.

The majority of the patients under discussion were free from emphysema and any marked degree of cyanosis. As indicated, the only patient (Case 10) with demonstrable organic cardiac disease had an oxygen saturation during the asthmatic attacks of 99 per cent; in Case 13 it was 90 per cent, and, in Case 20, in which there were a fairly marked degree of cyanosis and roentgenologic evidence of moderate emphysema, accompanied by a lung cyst, 84 per cent. This last patient falls into the category described by Meakins and Davies.<sup>14</sup> It is conceivable that, under certain circumstances, when the myocardium is already affected, moderate degrees of anoxemia may contribute to the development of electrocardiographic abnormalities, but not necessarily be fundamentally responsible for them. A capacity for adaptation to a conspicuous degree of anoxemia without the development of any cardiac abnormalities is commonly noted in cases of asthma and emphysema.

2. *Epinephrine*.—Electrocardiographic changes after the administration of epinephrine have been attributed by Wiggers<sup>15</sup> and Fowler, Hurevitz, and Smith<sup>16</sup> to anoxemia of the myocardium resulting from constriction of the coronary vessels. In animals these alterations consist of directional changes in the T waves, "W" forms of the QRS



complexes, and elevation of the P-R segment.<sup>17-19</sup> The injection of epinephrine, however, is not always followed by constriction of the coronary vessels.<sup>20, 21</sup> According to Gollwitzer-Meier and Krüger,<sup>22</sup> epinephrine causes coronary dilatation.

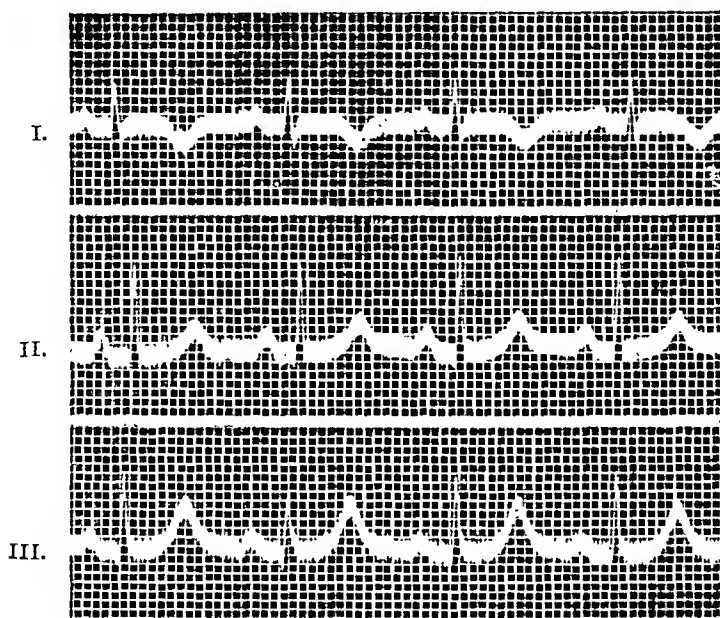


FIG. 6.—Case 19, Group 3. D. C., female, aged 36 years. Record taken June 29, 1936, shows deep inversion of T<sub>1</sub>.

In view of the fact that the effects of epinephrine injections on the electrocardiogram are transitory, and the records in our cases were often made during intervals when the patients were relatively comfortable, several hours after they had received epinephrine, it is questionable whether this drug had anything to do with the electrocardiographic changes which were noted. In Case 9 (F. H., Group 2), injections of epinephrine in oil twice daily to control residual wheezing after the subsidence of the acute attacks caused no abnormalities in the electrocardiogram, although changes in the auricular and ventricular complexes were present during the major asthmatic attacks. This is especially notable in view of the prolonged action of epinephrine in oil. In Case 7 (R. K., Group 2), in which high P waves appeared during an asthmatic attack, the administration of 0.3 c.c. of a 1:1,000 solution of epinephrine not only controlled the asthmatic paroxysm, but also caused reversion of the P wave to a normal level within five minutes. Repeated epinephrine injections in this patient while he was free of asthma had no effect on his electrocardiogram (Fig. 2).

3. *Positional Changes of the Heart.*—Master<sup>23</sup> and other investigators have reported low QRS waves in Lead I and right axis deviation in normal subjects with low diaphragms and mesially placed hearts. The roentgenograms of the twenty patients with electrocardiographic changes herein reported were reviewed. Only one patient showed a typically mesially placed heart. This patient had emphysema, a lung

cyst, and continuous asthma. In the remaining nineteen cases in this series, with the exception of Case 10, in which there was hypertrophy of the right and left ventricles, the hearts were of normal configuration. All the roentgenograms were taken while the patients were having asthmatic attacks.

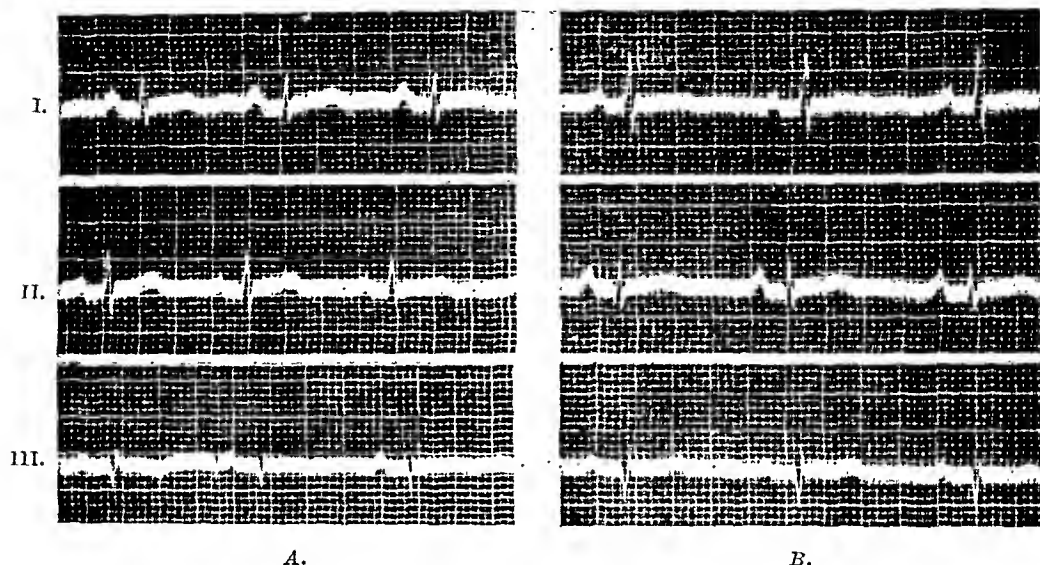


Fig. 7.—Case 20, Group 3. G. E., female, aged 48 years. A, record taken Dec. 1, 1939, shows QRS of low voltage. B, Record taken April 26, 1940, shows  $T_1$  and  $T_2$  lower.

The numerous allusions in the literature to a tendency toward right axis deviation in bronchial asthma may be attributed to positional changes as a result of a shift of the electrical axis toward the vertical plane. This, nevertheless, does not exclude the possible occurrence of right ventricular hypertrophy in cases of long-standing bronchial asthma, with frank right axis deviation in the electrocardiogram.

4. (a) *Allergic Response in the Lungs*.—A review of the pulmonary manifestations in the cases under investigation showed nothing in ten of the cases, interstitial infiltration in six, and emphysema and lung cysts in four.

In the ten cases in which no pulmonary lesions were demonstrable by roentgenologic examination, it may be assumed that the allergic reaction was essentially confined to the bronchi. Repeated attacks in such cases lead to hypertrophy of the bronchial musculature and various productive changes, including thickening of the bronchial blood vessels, as pointed out in autopsy studies by Huber and Koessler<sup>24</sup> and others. In the six patients with pulmonary infiltration, the development of the lesions was insidious in onset, and migratory, exudative, interstitial, and miliary in distribution, simulating tuberculosis. It was accompanied by fever ranging between 100° and 102° F., cough, asthma, and sputum eosinophilia. Often the changes in the lungs could not be detected on physical examination alone. Similar pulmonary infiltra-

tions, but without asthma, have been recorded by Löffler,<sup>25</sup> Engel,<sup>26</sup> Cole and Korns,<sup>27</sup> Vaughan and Hawke,<sup>28</sup> and others. Vaughan and Hawke, as well as Cole and Korns, regarded the pulmonary lesions in their cases as expressions of a more or less disseminated "angioneurotic edema" due to food allergy. The absence of asthma in the majority of the cases reported indicates that allergic inflammatory reactions in the lungs may occur independently of bronchial asthma, a fact which has been proved experimentally. Although the nature of the pulmonary lesions in our cases cannot be established unequivocally, the probability is that they represent hyperergic forms of response, in which interalveolar capillaries, the larger vessels, and the associated mesenchymal structures participate. The resultant interstitial edema and cellular infiltrations could account for the peculiar roentgenographic appearance and paucity of physical signs. In support of this view the following observations may be offered. First, the roentgenographic shadows were not homogeneous, like those produced by pneumonia; second, their miliary and interstitial character suggested a hematogenous rather than an alveolar distribution; third, their appearance with the outbreak and disappearance with the termination of the asthmatic paroxysm and sputum and blood eosinophilia suggested not only a reversibility common to allergic vascular reactions, as in urticaria, but also the participation of a common allergic excitant. Autopsy observations in two of a group of cases reported by one of us (J. H.)<sup>1</sup> in which there were similar clinical manifestations disclosed that the interstitial lesions in one patient, aged 11 years, consisted of cellular infiltration of the interalveolar septa with lymphocytes, eosinophiles, and polymorphonuclear cells, fibrosis, and edema, as well as arteritis of the pulmonary vessels. Other important organs were the seat of periarteritis nodosa. In the second patient, aged 36 years, the small vessels of the lung were thickened, and the vessels of the heart, pericardium, and liver showed evidence of periarteritis nodosa. Thickening of the pulmonary arterioles, giving rise in some places to endarteritis obliterans, was also reported by Kountz and Alexander<sup>29</sup> in a patient, aged 48, with long-standing asthma, who did not have diffuse hyperergic vascular disease. It would seem, therefore, that changes in the vascular system of the lungs in asthmatic patients may vary, not necessarily with the age of the patient, but with the tempo of the allergic process.

In cases in which the allergic tissue reactions recur, the erstwhile reversible process may become irreversible, and organization, with fibrous tissue formation appearing in the roentgenogram as interstitial fibrosis, may ensue. A comparable train of events results in the production of the so-called hyperplastic sinusitis, after repeated sinus attacks in chronic asthmatic patients. The pulmonary fibrosis may cause emphysema, as noted in two of the cases, and lung cysts probably

result from rupture and coalescence of emphysematous blebs; this was also evident in two other cases in this series.

4. (b) *Cardiac Reactions Following Sensitization.*—Numerous investigators have reported that electrocardiographic abnormalities occur in experimental animals during anaphylactic shock. These changes consisted of disturbances of conduction and abnormalities in the origin and spread of the electrical impulses. They have been attributed by some observers to anoxemia of the myocardium, and, by others, to toxic substances elaborated during the shock. Wilcox and Andrus<sup>30</sup> demonstrated various electrocardiographic abnormalities, including prolongation of the P-R interval, changes in the form of QRS complex, directional changes of the T wave, ectopic rhythms, and auriculoventricular dissociation, with ventricular tachycardia, when the perfused, isolated hearts of guinea pigs which had been sensitized to horse serum were exposed to small amounts of homologous antigen. These abnormalities were ascribed to coronary insufficiency because there was a striking reduction in the rate of coronary flow.

In the hearts of two patients who died during serum sickness, Clarke and Kaplan<sup>31</sup> found histologic changes which resembled those which occur in animals when protracted anaphylaxis is induced by foreign serum. These lesions were of a hyperergic nature, and consisted of proliferation of histiocytes in the intima of the large vessels and necrotizing arteritis and periarteritis of the smaller coronary arteries.

In view of these experimental and pathologic observations, the question arises whether the electrocardiographic abnormalities in certain cases of bronchial asthma may not represent allergic responses in the pulmonary and coronary vessels to the agents implicated in the production of the asthmatic seizures. Since, in the cases studied, neither epinephrine nor positional changes of the heart could be regarded as responsible for the electrocardiographic abnormalities, the problem becomes one of the relative roles of allergic reactions in the lungs and heart and associated anoxemia.

Despite the variations in the cardiac responses to oxygen want, the oxygen deficit which is necessary to produce electrocardiographic changes in normal subjects, as has been noted above, seems to be much greater than that commonly encountered in the average asthmatic patient with an intact heart. Observations on the arterial anoxemia in three of the cases did not indicate any high degree of oxygen unsaturation. Pending further investigation of arterial oxygen saturation (now in progress), definite conclusions as to the exact relationship between oxygen want and the electrocardiographic abnormalities in cases of asthma must be held in abeyance.

#### SIGNIFICANCE OF P-WAVE CHANGES

Inasmuch as the cardiac diseases which usually cause abnormalities of the P waves, such as mitral stenosis and congenital heart disease,

could be excluded, it may be assumed that the high voltage of the P wave in these cases depended on an extracardiac factor. In view of the fact that the high P waves appeared during asthmatic seizures and disappeared with their recession, they may be regarded as indicating that a transitory increase in the tension in the lesser circulation was associated with the asthmatic paroxysm. Since the latter was an allergic phenomenon, it would be reasonable to assume that the factors involved therein would likewise play a role in the augmentation of the vascular tension. Accordingly, the currently accepted theory of the mechanism involved in the allergic response, which implies the liberation of certain injurious agents of a histamine-like character on or within the tissue cells consequent upon an antigen-antibody interaction, may be utilized in explaining the phenomena observed. If we accept the contention of one group of investigators,<sup>32, 33</sup> who claim that the effect of histamine products is one of constriction of arterioles and dilatation of capillaries, associated with increased permeability, it is conceivable that, with the elaboration of such, or similar, substances during asthmatic attacks, spasm of the pulmonary arterioles, as well as increased dilatation and permeability of the interalveolar capillaries, may ensue. To this may be added contraction of the bronchi, which is another effect of histamine. If the constriction of the vessels is sufficiently marked it may interfere with the pulmonary circulation, and the tissue edema which results from the increased vascular permeability may act as a tamponade, and add to the burden of the pulmonary flow. The resulting obstruction to the circulation in the lung could give rise to hypertension of the lesser circulation. Such an increase of tension would augment the load of the right ventricle, and, when transmitted to the right auricle, would be reflected in the electrocardiogram by increased voltage of the P waves.

This sequence of events, namely, hypertension of the lesser circulation, followed by encroachment upon the integrity of the right side of the heart, finds its analogue in the spasmodic contraction of the pulmonary vessels and the resultant dilatation and failure of the right side of the anaphylactic rabbit's heart.

The high P waves disappeared in five of the cases when the attacks of bronchial asthma subsided, which suggests that the pulmonary vascular abnormalities are reversible. They likewise returned to normal in Case 7 (R. K., Group 2) after the administration of adrenalin. In this instance it may be assumed that the epinephrine relieved the tissue edema and the bronchospasm brought about by the released "H" substance, thus reducing the intra-auricular tension. The antagonism of epinephrine and histamine is well known.

Confirmatory evidence of pre-existing hypertension of the lesser circulation was obtained at the autopsy on S. B. (Case 11, Group 2), whose electrocardiogram had shown recurrently high P waves. This consisted of thickening of the walls of the pulmonary vessels and mod-

erate hypertrophy of both the right auricle and ventricle. It is significant that roentgenologic examination of this patient shortly before her death showed no gross abnormalities in the cardiac silhouette. Searff,<sup>34</sup> who studied the effects of ligation of the left pulmonary artery in dogs, found a temporary increase of 30 to 50 per cent in the pulmonary systolic pressure, and 35 to 100 per cent in the diastolic pressure. These pressures subsequently returned to normal. Three or four months later, no increase in the size of the heart was detectable by the usual roentgenologic examination, although at autopsy the right ventricle was found to be distinctly heavier than normal. From these observations it would seem that the ordinary roentgenographic or fluoroscopic examination cannot disclose early, moderate changes in the size of the myocardium which would suggest, in the absence of the usual, known, responsible factors, an alteration in the tension in the pulmonary circulation. The presence of a high P wave, therefore, in the light of the experimental observations of Searff and the autopsy observations in the case under discussion, must be regarded as *one of the earliest indications* of increased tension in the lesser circulation.

The persistence of high P waves in repeated electrocardiograms in Cases 3, 10, and 12 could be attributed to a permanent increase of tension in the lesser circulation caused by the emphysema and lung cysts which were demonstrated by clinical and roentgenologic examination in two of these patients. Inasmuch as the degenerative tissue changes which are associated with emphysema are usually combined with a reduction of the vascular bed, it may be inferred, in the light of our hypothesis, that the latter is a result of irreversible allergic reactions in the blood vessels of the lungs.

#### AURICULAR AND VENTRICULAR ELECTROCARDIOGRAPHIC CHANGES

Only one patient (Case 10) who had enlarged P waves, small and slurred QRS waves, and inversion of  $T_2$  and  $T_3$ , showed roentgenologic evidence of right- and left-sided cardiac enlargement. In this case, hyperergic vascular disease, characterized by perivascular infiltration, with eosinophilia suggestive of the preliminary stages of periarteritis nodosa, was demonstrated in biopsy sections of a nodule in the conjunctiva. The persistence of the electrocardiographic abnormalities in this case during asthma-free intervals, as well as the permanent increase in the size of the heart, indicated that these changes were not dependent upon anoxemia caused by the asthmatic paroxysms, but, in all probability, reflected irreversible hyperergic responses in the coronary vessels to allergenic stimulation. Actual determination of the arterial oxygen tension of this patient's blood during one of her asthmatic seizures showed that it was 99 per cent saturated.

In contrast to these permanent alterations were the similar, but reversible, electrocardiographic changes in Cases 8 and 9 of this group. These patients likewise presented signs and symptoms of generalized

hyperergic vascular disease, which, however, did not progress with the rapidity and intensity as in Case 10, and tended toward remission. Thus, Patient 8, who presented the signs of periarteritis nodosa, became completely well while under observation, in spite of the peripheral neuritis, the eosinophilic peritonitis, and the subsequent intestinal infarction which was attributed to arteritis of one of the mesenteric vessels. The recovery, which was possibly temporary, probably occurred because the hyperergic vascular process was reversible. A similar favorable issue was observed in Case 9, with termination of the acute pericarditis, urticaria, and fugitive joint swellings. While the latter symptoms prevailed, the asthma which preceded their onset vanished, only to return with the recession of the pericarditis, urticaria, etc., illustrating a shift in shock organs which is common in allergic states. The electrocardiographic abnormalities which were originally ushered in with the asthmatic paroxysm remained unaltered during the development of symptoms in the other shock tissues. The restoration of the electrocardiograms to normal with the complete recovery of both of these patients signaled a remission of the allergenic stimulation which was basically responsible not only for the asthma, but also for the manifestations in the other organs. Thus the manner of development and the course of the symptoms in these three cases would tend to support the theory that the electrocardiographic changes were in all probability due to various degrees of allergic reactions in the coronary vessels, such as spasm and edema, with secondary ischemia of the myocardium, rather than the result of primary oxygen want associated with asthma. Except for the fact that the tissue responses in the other seventeen cases in this series were limited to the lungs and heart, the identity in symptomatology suggests a similar pathogenesis in the evolution of the pulmonary and electrocardiographic abnormalities.

#### VENTRICULAR CHANGES

It is well known that aberrations of the QRS complex and RS-T segments as well as T-wave changes, may result from pericardial involvement, myocardial damage brought about by local anoxemia consequent upon coronary artery constriction, such as is associated with coronary occlusion, or the direct toxic effects upon the myocardium of such systemic diseases as diphtheria or rheumatic fever. Since the ventricular electrocardiographic changes in many of our cases showed a direct temporal relationship to the occurrence and subsidence of both the asthmatic attacks and pulmonary infiltration, they may also be considered as manifestations of various degrees of allergic response in the vessels of the heart, with resultant coronary insufficiency and myocardial ischemia. Such a view, taking into consideration the theoretical explanation given above in respect to the allergic reaction, would also imply the mediation of a histamine-like substance. This

concept finds support in the investigations of Weiss, et al.,<sup>35</sup> who described T-wave changes in human beings after the intravenous administration of small doses of histamine solution, and also in the experimental observations of Ewert and Kallos<sup>36</sup> on guinea pigs after the inhalation of finely divided histamine. The inversion of T<sub>1</sub> in Case 19, of Group 3, may be interpreted as a manifestation of a mechanism similar to that described by these observers. On the day that the record was taken, this patient had no asthma and was devoid of any clinical manifestation of anoxemia. She left the hospital improved, only to return five weeks later in status asthmaticus. She died after an injection of morphine. Except for emphysema and right-sided cardiac dilatation, with hypertrophy, autopsy failed to disclose any gross changes in the myocardium or coronary vessels. Microscopic examination, however, showed scattered foci of myofibrosis in the left ventricle and perivascular fibrosis at the apex, in addition to endocardial thickening of the left auricle. Similar lesions have been observed in coronary insufficiency in patients with narrowed but patent arteries, as well as after certain systemic infections.\* In the absence of either of these factors the possibility that the allergens responsible for the asthmatic attacks may have acted through the mechanism of a histamine release upon the coronary vessels and capillaries, giving rise to the electrocardiographic changes, as well as the histologic lesions, should not be dismissed.

#### CONCLUSIONS

In summarizing these various observations the following deductions seem to be pertinent.

There was no clinical indication or laboratory evidence from study of the oxygen saturation of the blood in three cases of this group that respiratory anoxemia was the primary factor in inducing the electrocardiographic changes which were observed. Moreover, the relative unimportance of respiratory anoxemia was also illustrated by the fact that, in Cases 8, 9, and 10, the electrocardiographic abnormalities persisted during asthma-free periods, when hyperergic manifestations were developing in other shock tissues. The temporal relationship between the appearance and disappearance of the pulmonary lesions, the electrocardiographic changes, and the involvement of various other shock organs implies a common underlying mechanism. Although there was no involvement of shock tissues other than the heart and lungs in the remaining cases, the common association of electrocardiographic disturbances and pulmonary involvement with asthma, the same as in Cases 8, 9, and 10, suggests a similar pathogenesis.

The simultaneous occurrence of deviations in the auricular and ventricular complexes may be explained in two different ways:

\*Personal communication from Dr. Henry Horn.



(a) They may be caused by coronary insufficiency, brought about through compression of the right coronary artery because of a rise in intraventricular pressure<sup>37</sup> consequent upon an increase in tension in the lesser circulation. The latter may be considered the result of allergic vascular reactions in the lung. Such a mechanism could account for the high P waves, as well as changes in the QRS and T waves. These changes would necessarily be reversible, and be dependent on the presence or absence of hypertension in the pulmonary circuit and the asthmatic paroxysms.

(b) They may indicate not only hypertension of the lesser circulation, but also the development of allergic reactions in the coronary vessels, such as spasm and edema, leading to insufficiency. The reversibility or irreversibility of the electrocardiographic deviations would therefore depend on the character of the exciting agent and the intensity and extent of the allergic response.

#### SUMMARY

1. Twenty of a series of fifty patients with bronchial asthma presented electrocardiographic abnormalities, such as tachycardia, axis deviation, high P waves, and QRS, RS-T, and T-wave changes.

2. Pulmonary infiltration appeared during the asthmatic paroxysms in six cases and disappeared in five. These infiltrations were regarded as manifestations of allergic reactions in the vessels and interstitial tissues of the lung.

3. The electrocardiographic abnormalities were reversible in nine cases and irreversible in five. The remaining six patients could not be followed. The reversible electrocardiographic changes appeared and disappeared in the majority of cases at the same time as the pulmonary lesions and asthmatic attacks.

4. The simultaneous occurrence of the pulmonary and cardiac changes suggested a common pathogenesis.

5. Changes in the auricular complexes, characterized by an increase in the voltage of the P waves, were present in fifteen cases. These were interpreted as indicating increased intra-auricular tension secondary to hypertension of the lesser circulation brought about by allergic reactions in the vessels of the lung similar to rabbit anaphylaxis.

6. Electrocardiographic abnormalities in the ventricular components were observed in fourteen cases. They were reversible in eight cases and irreversible in three. The remaining patients could not be kept for observation. The occurrence of these abnormalities in three cases during asthma-free intervals indicated that they were independent of respiratory anoxemia. That they may have been due to hyperergic reactions in the coronary vessels is highly probable, in the light of the clinical course. This was indicated by the involvement of numerous

shock tissues of a vascular nature, and the perivascular eosinophilic infiltration found in the biopsy sections of the conjunctiva in Case 10 as well as similar lesions in the skin of Case 8.

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## Department of Clinical Reports

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### RECENT MYOCARDIAL INFARCTION FOLLOWED BY INVOLVEMENT OF THE JOINTS OF THE HAND AND WRIST

#### A REPORT OF THREE CASES

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THREE cases in which myocardial infarction was followed by unusual involvement of the joints, particularly of the right hand and wrist, were seen by us recently. Since we have been unable to find any report of a similar sequence of events, we desire to draw attention to it because it may be more than coincidental.

#### CASE REPORTS

CASE 1.—H. R., a 53-year-old, married, white man, with a history of arthritis and rheumatism thirty years earlier, first noted attacks of dyspnea and precordial pain while on a trip to California. He remained in bed for one week, and, on his return home a week later, again complained of the same symptoms, which had increased in severity. He was hospitalized immediately. On admission, his temperature was 97.2° F.; his pulse rate, 88; his respiratory rate, 32; and his blood pressure, 96/78. Both the pulse and respirations were irregular. Physical examination revealed that the patient was pale and dyspneic; he was complaining of pain over the precordium. The heart was enlarged to the left on percussion; there were no cardiac murmurs; and the heart tones were of good quality. The lungs were normal. The liver was 3 fingerbreadths below the costal margin. Further physical examination revealed no abnormalities.

During the next few days he was markedly dyspneic and cyanotic, and had Cheyne-Stokes breathing. His temperature rose as high as 102° F., and the leucocyte count rose to 13,500. The blood pressure remained about 104/80. The electrocardiogram showed evidence of a recent anterior myocardial infarction in the healing stage. His convalescence was complicated by occasional attacks of precordial pain. There was present at this time a diffuse apex beat which suggested cardiac aneurysm, but this could not be confirmed by fluoroscopic examination.

Eight weeks after the onset of his myocardial infarction, he suddenly developed, for the first time, pain in the right metacarpophalangeal and carpal joints, associated with stiffness and swelling, but without redness or local heat. He was unable to flex the joints or to approximate the thumb to the little finger. Subsequently the right shoulder became involved, with pain, slight swelling, and limitation of motion. A month after the onset of the swelling in the right hand, a similar condi-

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tion developed in the left hand, although to a lesser degree, and involved principally the fingers. The recovery of the left hand was more rapid than that of the right. The swellings were treated with local heat and Crowe's vaccine. About eight months after the beginning of these joint symptoms he had improved sufficiently to drive his own car. He died suddenly two months later. No autopsy was performed.

CASE 2.—M. D., a 55-year-old, married, white man, with an essentially negative past history except for extrasystoles intermittently during the preceding ten years, and two attacks of renal colic within the preceding two years, was suddenly seized with an attack of severe, squeezing pain across the chest. Examination at this time revealed a pulse rate of 92 and a blood pressure of 160/110. The electrocardiogram two days later showed definite changes as compared with a curve taken five years before, and, with subsequent curves, suggested posterior myocardial infarction. There were continued fever up to 102° F. and a leucocytosis, accompanied by a fall in blood pressure to 80/60; the clinical manifestations were therefore also suggestive of myocardial infarction. The blood Wassermann and Kahn reactions were negative. During his convalescence, while at rest in bed, he had repeated attacks of precordial distress, together with paroxysmal auricular fibrillation; the latter was controlled with quinidine. After one such attack he developed pain in the right side of the chest, with râles at the right base posteriorly, which was thought to be caused by pulmonary infarction.

Two months after the beginning of the myocardial infarction, pain, swelling, and limitation of motion appeared in the small joints of the right hand and wrist. No redness, local heat, or systemic reaction accompanied the swelling. These signs in the right hand persisted for four months, subsiding gradually. Because of the diffuse apex beat and cardiac enlargement to the left on percussion, aneurysm of the ventricle was suspected, although this could not be confirmed fluoroscopically. He had occasional attacks of precordial distress for the next six months, but there was no recurrence of the swelling and stiffness of the right hand. He died suddenly while on a business trip, twelve months after the onset of his myocardial infarction. No autopsy was performed.

CASE 3.—B. L., a 72-year-old, white woman, had a history of frequent attacks of pain in various joints, including the shoulders and wrists, and showed roentgenologic evidence of hypertrophic arthritis of the cervical and dorsal spine. She had had hypertension for at least ten years. Her present difficulty began with a sudden attack of precordial pain, radiating down the right arm and associated with nausea, vomiting, and a fall in blood pressure. The temperature was 100.6° F., and the leucocyte count, 12,000. Râles were present at the bases of the lungs. She continued to have frequent attacks of pain over the precordium while at rest in bed. The electrocardiograms confirmed the clinical impression of myocardial infarction. Pain and swelling of the right carpal and metacarpal joints, without redness or local heat, developed six weeks after the onset of this attack. Soon the left hand was similarly involved, but to a lesser degree. During the height of the swelling there was marked limitation of motion. In the next five months the swellings of the hands gradually subsided, with the aid of local heat and massage. A year and a half later she developed another attack of severe substernal pain, typical of myocardial infarction, which led to her death in three days. No autopsy was performed.

#### DISCUSSION

These cases were striking in that the principal involvement occurred in similar joints in all three, and with about the same latent period after the onset of the myocardial infarction. Clinically, the process

resembled a periarthrititis or fibrositis, rather than an intra-articular arthritis. The phalangeal and metacarpal joints were mainly involved; the carpal joints were affected to a lesser extent. The tissues about the joints became slightly fibrosed and tight to a rather uniform degree. The skin overlying the joints was tense and glistening, but not reddened. Flexion was very difficult. In each case the pain associated with the acute cardiac attack radiated down the right arm, although in one instance it also radiated down the left arm, but with less severity. In no case was there any history of previous involvement of the affected parts by a similar process, but in two cases there was a past history of arthritis and rheumatism.

One can only speculate as to the etiology. In cases in which joint symptoms occurred shortly after the myocardial involvement, Libman<sup>1</sup> refers to the toxic effect of the necrosis on joints which were perhaps sensitized by gout or some other cause. In our cases the latent interval between the infarction and the joint involvement seems too long for this explanation. Libman<sup>2</sup> also refers to underlying metabolic disorders and suggests that sensitization of the joints by such disorders may play a role in the pathogenesis of this phenomenon. Two of our patients had a history of arthritic attacks in various joints. Edeiken and Wolferth<sup>3</sup> refer to shoulder pain after myocardial infarction and suggest an analogy to causalgia, although in their cases there was no evidence of trophic or vasomotor changes. Our patients did show what may have been a trophic disturbance. Edeiken and Wolferth refer to Howard,<sup>4</sup> who reported periarthrititis of the shoulder in cases of cardiac pain. Boas and Levy<sup>5</sup> reported cases of shoulder pain associated with angina pectoris and myocardial infarction. They suggest that sensitization of a dermatome by another disease might perhaps determine the site of radiation of pain. Summation of previous slight pain, plus cardiac pain, may be a factor. Extracardiac lesions, such as dental abscesses or spondylitis, are known often to determine the site of radiation of anginal pain.

It was noted in all our cases that the pain during the acute attack radiated down the right arm, which was the principal extremity involved. The possibility of a trophic disturbance following reflex vasomotor changes caused by the radiation of pain down the extremity has to be considered. The severe pain in the right arm may have contributed to subsequent inactivity and lack of use. Prolonged disuse will cause fibrosis about a joint, followed by bone and joint atrophy.<sup>6</sup> Atrophic changes in bones and in attachments about joints caused by lack of use have often been described.<sup>7</sup> Sudeek<sup>8</sup> attributed acute bone atrophy resulting from trauma to a reflex neurotrophic phenomenon.

The question of gout comes to mind. It is established that the orifices of the coronary arteries are frequently found to be occluded by atheromatous processes in cases of gout.<sup>9</sup> Unfortunately, however, neither

roentgenograms nor blood uric acid studies are available. It is hoped that such studies will be made in future cases.

The fact that all these patients died within a year of the acute cardiac attacks makes one wonder if any prognostic significance is to be attached to this sequence. These cases, coming so close to one another, have aroused our interest, and we are reporting them in the hope that others who may see similar cases may obtain further information, as we expect to do, to make possible better judgment of the prognosis and a better idea of the mechanisms involved in the syndrome.

We wish to express our thanks to Dr. Louis N. Katz for his suggestions in preparing this report.

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## CORONARY DISEASE IN THE APE

G. W. MANNING, M.D., TORONTO, CANADA

FOX<sup>1</sup> and Cowdry<sup>2</sup> have discussed general arteriosclerosis, including a brief description of coronary artery sclerosis in the higher monkeys and apes. Fatal coronary thrombosis, however, does not appear to have been observed. Consequently, the sudden death of an ape, shown at autopsy to have been caused by coronary thrombosis, is of particular interest in that it illustrates that coronary artery disease in the ape can progress to actual thrombosis, with sudden death, in a manner comparable to that observed in man. The history and post-mortem observations in a case of coronary thrombosis in an 8-year-old female ape are presented in this report.

### CASE REPORT

*History.*—"Lizzie," prior to her sudden death, was apparently in good health; she was well developed, was well nourished, and had always been quite active. She was a pleasant, intelligent ape and the favorite of the keeper. She had not suffered from any illness prior to Nov. 23, 1939. There was no history of previous falling or shortness of breath. Menstruation had been regular and normal for the preceding two years. Although she copulated regularly and frequently, she had never become pregnant.

On the morning of November 23, Lizzie was sitting on her platform about 6 feet above the cage floor. She had refused her usual morning treat, a stewed fig. The keeper was leaving the cage when he heard a terrific din, and turned to see Lizzie howling and then fall to the floor of the cage, where she rolled over on her back, breathing with great difficulty. The dyspnea became progressively more severe; the animal died in about six minutes, with some terminal, isolated, spasmodic gasps.

*Post-Mortem Examination.*—The body was that of a large, well-developed ape. With the exception of the chest, the examination revealed nothing of interest. Examination of the uterus revealed that she was not pregnant at the time of death. When the chest was opened, the lungs appeared dark and heavy. There was no free fluid or blood in the pleural cavity. The heart and lungs were removed together. There was no gross evidence of necrosis, cavitation, or tuberculous disease in the lungs. The parenchyma was resistant to cutting, and the raw surface was moist. Pressure on the lung tissue expressed somewhat frothy, pink fluid into the bronchi and on to the cut surface. Examination of the pulmonary arteries revealed no gross evidence of embolism.

The pericardium was slightly dull in appearance. When the pericardial sac was opened, a moderate amount of unclotted, bloody fluid was found. The heart appeared soft and slightly enlarged. The anterior surface was fresh and glistening, with a considerable accumulation of fat toward the base. The posterior surface of the left ventricle showed a definite abnormality. In one area (Fig. 1) the peri-

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cardium was adherent to the heart muscle, but, by careful dissection of the granulation tissue which had formed (a few fibrous strands had to be divided), a large infarcted area was revealed. The heart measurements were as follows:

|                              |          |
|------------------------------|----------|
| Width at base of ventricle   | 10.0 cm. |
| Length (apex to A-V sulcus)  | 7.8 cm.  |
| Diameter of aorta            | 1.3 cm.  |
| Diameter of pulmonary artery | 1.3 cm.  |

The infarct, which measured 4.5 cm. by 2.5 cm., was soft and elevated. It had the appearance of fleshy granulation tissue superimposed on a fibrous base and surrounded by similar, but older, scar tissue. On cutting, the older infarct was found to be quite superficial. Just proximal to this area a recent hemorrhagic infarct was seen.



Fig. 1.—Posterior surface of heart.

The coronary arteries were injected with a calcium carbonate, linseed oil mass, which ran into the arteries readily with a little pressure, and was observed to flow into the large veins within a few seconds. When slightly more pressure was applied, the mass flowed freely into the left ventricle. Following this, a careful dissection of the coronary arteries was carried out. As the injection mass traveled along the circumflex branch of the left coronary artery it ran out into the heart muscle in the area of the recent infarct. The coronary artery leading to this area was readily opened, and, in the gross, did not appear to be atheromatous or narrowed. However, at the margin of the infarcted area the artery could no longer be traced as a single channel, but was found to be ruptured, allowing the injection mass to flow freely into the heart muscle. There was a wide separation of the muscle fibers in this area, indicating that the recent infarct had extended throughout the entire

thickness of the posterior ventricular wall. The myocardium in this area was soft and friable. The injection mass was scattered throughout this region, and no definite outline could be found. In general, this area appeared to be roughly oval, and about 2 cm. by 4 cm. in size. The endothelium of the remaining coronary arteries appeared smooth and glistening; there was no gross evidence of thickening, narrowing, or atheromatous changes.

*Microscopic Observations.*—Sections were taken from the liver, lungs, and numerous areas of the heart. There was marked congestion of the lungs. The blood vessels were engorged, and, in many areas, the bronchi were filled with a mixture of erythrocytes and pale-staining fluid (Fig. 2). The bronchial mucosa appeared thickened and edematous.

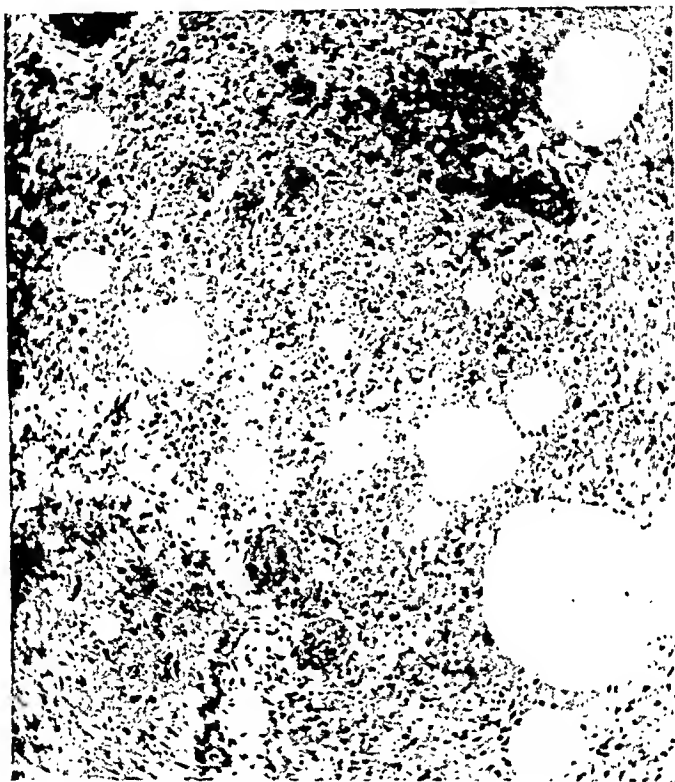


Fig. 2.—Photomicrograph of section of lung.

Sections taken from the liver showed evidence of acute congestion. In many areas there was hemorrhage in the central vein areas. Venous congestion in the portal areas was also found.

Microscopic examination of the older infarcted area on the posterior surface of the heart revealed a superficial area of granulation tissue, superimposed on fibrous tissue. The deeper branches of the coronary artery in this area were completely occluded by fibrous tissue (Fig. 3). In the area of the recent infarct (Fig. 4) there was a wide separation of the muscle fibers, resulting from the marked extravasation of blood. (Since the heart was perfused, few, if any, erythrocytes could be seen in this area.)

Further evidence of coronary artery disease was manifested, both in this area and other sections taken from the heart, by a considerable degree of intimal thickening. Subendothelial proliferation could be seen, particularly in the medium and smaller coronary arteries (Fig. 5), resulting in narrowing of the lumen.



Fig. 3.—Photomicrograph of scarred area shown in Fig. 1. Note complete occlusion of coronary arteries and fibrous tissue at lower part of figure, deep to the superficial scarred area.



Fig. 4.—Section taken from freshly infarcted area.

## DISCUSSION

The gross and microscopic examination of the heart would indicate that this ape had had coronary artery disease prior to her sudden "cardiac" death. This view is supported by the fact that there were an area of myocardial fibrosis, a recent infarct, and evidence of intimal thickening of the coronary arteries. A reasonable sequence of events would appear to be that coronary artery disease, with intimal thickening, had progressed in this heart until, because of either marked narrowing or thrombus formation, an area of fibrosis occurred about the termination of a branch of the left circumflex coronary artery. Later, more

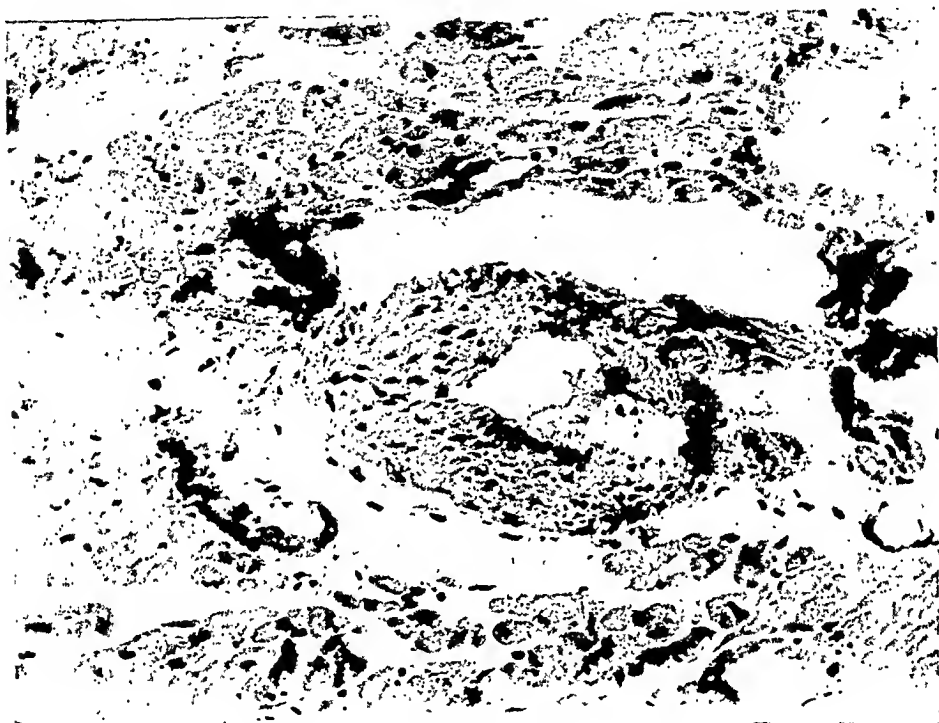


Fig. 5.—Section of myocardium and coronary artery, showing intimal thickening with narrowing of the lumen.

proximally in the same artery, a coronary accident, likely caused by rupture of a diseased and weakened vessel, resulted in sudden cardiac death. The possibility of thrombosis must also be considered, although no evidence other than the presence of a recent infarct (which may have been the result of hemorrhage) was found. It was decided to perfuse and inject this heart in the hope of demonstrating a thrombus and infarct. However, a well-developed collateral circulation made this difficult, and the fact (already mentioned) that the injection mass flowed freely into the infarcted area suggested that rupture of a coronary artery had occurred. Nevertheless, a loosely attached thrombus and weak vessel wall may have existed, but were not found after perfusion and injection. This experience strongly indicates that, when searching for evidence of coronary disease, such as thrombus formation, rupture,

etc., it is far better to dissect and section a heart carefully in the fresh state than to perfuse and inject the vessels.

It is interesting that the coronary artery distribution in this case was similar to that of the human heart. In many of the lower animals, particularly the dog, which is used a great deal in the experimental investigation of coronary occlusion, the distribution is significantly different from that in man. In the dog the right coronary artery is insignificant as compared to the left. The left coronary gives rise to both the anterior and posterior descending branches, and supplies the entire septum. In man and the ape the distribution of the right and left coronaries is of equal importance. The posterior descending is a branch of the right coronary artery, and the septum derives its supply from both the right and the left coronary arteries.

Since an experimental investigation of sudden coronary occlusion has been in progress in this laboratory for five years, the discovery of this case of fatal coronary thrombosis in the ape was of particular interest. After sudden ligation of a coronary artery in the conscious dog there are severe cardiac pain, cardiac irregularities, a fall in blood pressure, brief rigidity or convulsive movements, disappearance of pulse, congestion of neck veins, pallor, cyanosis, dilatation of the pupils, rigidity followed by muscular relaxation, a few deep gasps, and death of the animal. Therefore, it is interesting that in this case of coronary thrombosis in the ape the clinical signs were exactly comparable to those observed experimentally in the dog. Furthermore, published reports reveal that in human cases of sudden death caused by coronary artery occlusion the clinical signs and symptoms are also similar to those observed in the dog, and the nature of death is like that of the chimpanzee discussed in this paper. The pathologic observations were comparable to those in human cases of coronary thrombosis.

#### SUMMARY

An interesting case of coronary thrombosis in an 8-year-old female ape, in which the clinical signs, type of death, and pathologic changes in the heart were comparable to those in human cases of fatal coronary thrombosis, has been observed and described.

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## Department of Reviews and Abstracts

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### Selected Abstracts

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Green, H. D., and Wégria, R.: Effects of Asphyxia, Anoxia, and Myocardial Ischemia on the Coronary Blood Flow. *Am. J. Physiol.* 135: 271, 1942.

The effects of systemic and myocardial asphyxia and anoxia on the coronary circulation of dogs anesthetized with morphine and sodium barbital have been studied by metering, with an optically recording orifice-meter, rate of flow of blood from the aorta into a coronary artery, while the aortic head of pressure was measured by an optically recording pressure manometer. Both of these instruments were of adequate frequency to record the details of the contour of the flow and pressure fluctuation occurring within a single heart cycle.

Asphyxia produced by interrupting the artificial respiration and local ischemia produced by temporarily stopping the blood flow to an area of the myocardium caused increased coronary flow even in the absence of any change of aortic pressure. Since the responses to hypercapnia were negligible under the conditions of these experiments, whereas the effects of systemic anoxia (produced by artificial respiration with mixtures of air and nitrogen) and myocardial anoxia (produced by cyanide injections into the coronary artery) were essentially similar, it is concluded that they all depend upon the anoxia produced and probably upon the presence of this anoxia in the myocardium.

Since the ratio of flow to pressure—index of flow—was increased even more in systole than in diastole, it is concluded that the anoxia causes a relaxation of the wall of the coronary vessels and also alters the dynamics of the myocardium in such a way that the systolic tension development in the myocardium is less effective in producing the extravascular compressing force normally present during ventricular systole.

AUTHORS.

Caviness, V. S., Bell, T. A., and Satterfield, G. H.: The Correlation Between Blood Pressure and the Concentration of Sulfocyanates in the Blood. *North Carolina M. J.* 2: 585, 1941.

This study was undertaken to determine whether any correlation exists between natural blood sulfocyanate levels and blood pressure levels.

A total of 241 persons who had not received treatment showed (1) that each person has a fixed level of blood sulfocyanate which does not appear to change from week to week, (2) that natural blood concentrations of sulfocyanates range from 0.31 to 2.55 mg. per 100 c.c. of blood, and (3) that the average blood sulfocyanate level for each blood pressure group varies inversely with the blood pressure.

These findings suggest that sulfocyanates are the most important natural depressor substances in the human blood.

AUTHORS.

Cossio, P.: A New Model Stethoscope. *Rev. argent. de cardiol.* 8: 257, 1941.

A new model of chest piece for binaural stethoscope is described. It has the same size as those in general use and yet has a much greater amplifying power. The natural frequency of its resonating chamber may be changed at will, making it appropriate for the selective magnification of low- or high-pitched sounds.

After considering the characteristics of cardiac and pulmonary acoustic phenomena and the limitations of the ear, the author advocates the use of mediate auscultation in clinical study of the lungs as well as the heart.

AUTHOR.

Lieberson, A., Chasnoff, J., and Goldbloom, A. A.: Clinical Studies in Electrocardiography. IV. Value of Electrocardiogram in Coronary Thrombosis With Special Reference to Localization of Infarct. *New York State J. Med.* 41: 2032, 1941.

A correlative review of the clinical, electrocardiographic, and pathologic diagnoses was made in thirty-four patients (twenty-four men and ten women) who showed myocardial infarction at post-mortem examination. The autopsy material included sixteen cases of anterior infarcts, nine cases of posterior infarcts, and nine cases of combined anterior and posterior infarcts. Only sixteen of the thirty-four cases (47 per cent) were diagnosed by the electrocardiogram alone, the correct electrocardiographic diagnosis being made in eight cases of anterior infarct, seven of posterior, and one of combined infarcts. In the other eighteen cases the electrocardiogram did not show changes typical of infarction, but rather bundle branch or intraventricular block (eleven cases) and nonspecific myocardial damage.

In contrast, the clinical diagnosis before the electrocardiogram was taken was correct in twenty-six cases (76 per cent). When both the clinical and electrocardiographic evidence were used, the correct diagnosis of coronary infarction was made in thirty-one cases (91 per cent). The greater accuracy of the clinical as compared to the electrocardiographic diagnosis in these cases of proved coronary infarction emphasizes the prime importance of the history and clinical examination in the diagnosis of this condition, particularly in patients who suffer from old coronary thrombosis or sclerosis and who are not likely to have a characteristic electrocardiogram with the repeated infarctions.

AUTHOR.

Gillespie, J. E. O'N.: Pulmonary Venous Return Via the Superior Vena Cava. *Brit. Heart J.* 3: 241, 1941.

A case is described in which the only method by which blood could return from the lungs to the heart was through an opening into the superior vena cava. Communication with the left side of the heart was maintained by a patent foramen ovale.

It is believed that this abnormality has not been recorded previously.

AUTHOR.

Bramwell, C., and Jones, A. M.: Coarctation of the Aorta. The Collateral Circulation. *Brit. Heart J.* 3: 205, 1941.

The post-mortem findings in a patient with coarctation of the aorta who died from subarachnoid hemorrhage due to a ruptured cerebral aneurysm have been described.

As the coarctation had been diagnosed and the condition fully investigated two years previously, it was possible to compare the clinical and post-mortem findings.

Prior to autopsy the cadaver was injected with barium paste and the arterial anastomoses were studied radiographically.

The anatomy of the collateral circulation has been described. The factors that determine the distribution of rib notching and some possible causes of pain in this condition have been discussed.

AUTHORS.

Saphir, O.: Myocarditis: A General Review, With an Analysis of Two Hundred and Forty Cases. *Arch. Path.* 32: 1050, 1941, and 33: 88, 1942.

In an analysis of autopsy material comprising 5,626 cases, myocarditis was encountered in 240 cases (4.26 per cent). This material was taken from a general hospital, and no cases of contagious diseases were included. The more recent literature on myocarditis occurring as a disease entity or a sequela in infectious diseases is reviewed. Reports of fetal myocarditis are extremely rare. Myocarditis in contagious and infectious diseases, not necessarily associated with endocardial lesions, is discussed. Primary degenerative changes and secondary inflammation are found particularly in diphtheria, typhoid fever, and influenza (grip, "flu" and like conditions). Myocardial changes in scarlet fever are characterized by an involvement of the interstitial tissue, although the heart muscle fibers may also be replaced by inflammatory cells. Myocarditis occurring in instances of infection of the respiratory tract is discussed, myocarditis as occurring in pneumonia being stressed. Meager reference is also made to myocardial changes in measles, mumps, whooping cough, variola, varicella, paratyphoid, and dysentery.

Meningococcal myocarditis is characterized by a hemorrhagic exudate with the early appearance of endothelial leucocytes, destruction of muscle fibers, and presence of intracellular Gram-negative diplococci. Gonococcal myocarditis is often found in association with gonococcal endocarditis. Abscesses of various sizes may be present in the myocardium. Isolated involvement of the myocardium occurs in gonococcal infection. Myocardial changes are described in tularemia; the lesions are principally foci of necrosis with lymphocytic infiltrations.

The literature on isolated myocarditis is relatively extensive. Apparently the term "isolated myocarditis" denoted inflammatory changes in the myocardium of wide variety and of varied etiological background having in common an isolated and nonspecific involvement of the myocardium in the absence of inflammatory changes in the endocardium or pericardium and of unknown cause. Instances of isolated myocarditis may be divided into two groups—those in which there are more or less diffuse inflammatory lesions in the myocardium and those in which granulomatous lesions are present. Various etiological agents have been held responsible for these granulomas, and often syphilis or tuberculosis has been suspected but not proved to be the underlying condition. More recently a special form of hypersensitivity, particularly that due to arsphenamine, has been held responsible for this form of myocarditis. As long as the cause is not known the term "granulomatous" seems adequate. The diffuse form of isolated myocarditis is not characteristic histologically.

Myocardial lesions in association with subacute bacterial endocarditis are common. They consist of abscesses, diffuse acute inflammatory changes, particularly pronounced in the interstitial tissue and consisting mostly of infiltrations of polymorphonuclear leucocytes and lymphocytes, foci of perivascular infiltrations, and occasionally Aschoff bodies. Often minute organizing infarcts are encountered. Inflammatory changes are often present in the myocardium in instances of acute bacterial endocarditis. Foci of acute inflammatory changes, particularly pronounced in the interstitial tissue, are significant.



Although reports of abscesses of the myocardium are unusual, this study shows that such abscesses are common in instances of pyemia. Clinically, they are regarded as occurring terminally. The clinical symptoms of myocarditis and the type of death of the patient probably depend upon the number and the localization of the abscesses.

Although the explanation of rheumatic fever as a form of allergy is attractive, it is at best a hypothesis founded on animal experiments. If rheumatic fever is to be considered an allergic phenomenon, the Aschoff body must be discarded as the specific histologic stigma of rheumatic myocarditis. Thus the significance of the Aschoff body has aroused much discussion in recent years. However, from a critical review of the literature and from studies of many hearts it appears clear that rheumatic myocarditis is a specific disease entity, probably caused by a specific though unknown agent, the Aschoff body being the characteristic granuloma. Structures which do not conform to the classic description should not be definitely classified as Aschoff bodies although they may resemble them. Aschoff bodies so far have not been produced experimentally. There seems to be not a single instance on record of Aschoff bodies in association with Sydenham's chorea in the absence of rheumatic fever.

Myocardial changes occurring in the Libman-Sacks syndrome are also discussed briefly.

In regard to tuberculous myocarditis, three main types are differentiated, namely, the nodular, the miliary, and the diffusely infiltrative. The last should be accepted only if the histologic changes are undoubtedly characteristic of tuberculosis or if the presence of the tubercle bacillus can be demonstrated either by guinea pig inoculation or by staining methods. Involvement of the myocardium in Hodgkin's disease, to judge from the literature, is apparently rare. Extensions of mediastinal masses into the pericardium and the myocardium are occasionally seen in routine post-mortem material, although such occurrences are not especially reported. Rarely may the myocardium be involved in Boeck's sarcoid.

From the available literature and from a study of this subject over a period of fifteen years it must be concluded that in acquired syphilis the entity syphilitic myocarditis, characterized by diffuse syphilitic inflammation and the presence of spirochetes, is extremely rare if it occurs at all. In congenital syphilis, however, myocardial lesions with the presence of spirochetes are occasionally encountered. Gummas are rarely seen. In a very recent report it was stated that gumma in the myocardium was encountered in only five of 30,265 autopsies.

The myocardium may be involved in blastomycosis, actinomycosis, moniliasis, and sarcosporidiosis. The respective parasites are occasionally encountered in the myocardium. Likewise myocardial lesions are reported in toxoplasmosis and histoplasmosis.

Typhus myocarditis is not rare. According to a recent report, 97 per cent of patients who died of typhus showed inflammatory lesions in the myocardium. Such lesions are usually focal, rarely diffuse. Myocarditis is also seen in Rocky Mountain spotted fever; occasionally Rickettsia-like bodies are found in large numbers in the myocardium. Rarely does yellow fever produce myocarditis.

Among helminthic diseases, trichinal disease is the one with which myocarditis is most frequently associated. The myocardial lesion usually occurs between the fourth and the sixth week following infection; at least death from myocarditis occurs at that time. Histologically, the lesion is characterized by an involvement of both the parenchyma and the interstitial tissue and by foci of necrosis. Among the inflammatory cells the lymphocytes predominate, but often many eosinophilic leucocytes are also present, although their occasional absence is stressed. From experimental studies and some autopsies on human subjects it is clear that larvae are present in

the myocardium about a week from the time of infection and that they then disappear. It is therefore evident that the diagnosis of trichinial myocarditis is not necessarily dependent upon the finding of larvae in the myocardium. Mention is also made of the involvement of the myocardium in echinococcus disease.

From a review of the literature one must conclude that there are no consistent myocardial changes described in patients dying with hyperthyroidism and hypothyroidism. So-called myxedema myocarditis does not occur. Myocarditis caused by acute or chronic nephritis per se or by uremia is a myth. Degenerative changes may be found in the heart muscle in such diseases, as in any wasting or chronic infectious disease. Such vascular changes as are seen in the kidney in arteriolosclerosis or arteriolonecrosis (nephrosclerosis of either variety) may also occur in the myocardium. Uremic pericarditis may extend into the myocardium. Whatever may have caused acute nephritis may also have caused myocarditis.

Myocardial changes are described in vitamin deficiencies. Most of the available references concern beriberi. The principal changes in the myocardium are of a degenerative nature, but there also occurs a type of inflammation described as "serious inflammation." This is thought to be a reaction of the tissues to the presence of plasma outside the capillary wall. The plasma apparently injures the tissues, with the result that there is a gradual new formation of a thin, lacelike connective tissue.

AUTHOR.

**Moolten, S. E.: Prolonged Survival After Perforation of the Infarcted Interventricular Septum in Coronary Arterial Disease. Arch. Int. Med. 69: 108, 1942.**

Rupture of the left ventricle after infarction is immediately fatal unless the area of softening is situated in the interventricular septum. In the latter case death may be delayed several days and then occur as a result primarily of the severe shock and heart failure resulting from coronary occlusion. Prolonged survival is rare and is characterized by intractable right ventricular failure and the presence of the harsh systolic murmur of interventricular septal defect.

The interventricular septum considered as a functional entity is of particular significance, both as a component of deep muscle tracts common to both ventricles and as an agent for protecting the right ventricle by preserving the differential in pressure between the two ventricles.

AUTHOR.

**Keagy, R. M., and Magee, R. S.: Supraventricular Tachycardia in Infancy. Pennsylvania M. J. 45: 44, 1941.**

A case of supraventricular tachycardia in a 5-month-old infant is reported. The acute attacks were treated successfully by the subcutaneous administration of mechohyl; recurrence of attacks has been prevented by daily doses of digitalis.

AUTHORS.

**Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia. Arch. Int. Med. 68: 1074, 1941.**

The authors have studied the problem of the pulmonary changes in rheumatic fever from a different aspect, choosing their cases in consecutive order, eliminating none of them because of the absence of clinical or macroscopic evidences of pneumonia or consolidation. In this manner the authors believe the evolution of the entire pulmonary picture may be unfolded in chronologic sequence and the histologic

changes correlated with the approximate duration of the disease as determined from the clinical history. They have ascertained the duration of the illness at home before admission to the hospital, the time spent in the institution before death, and the number of previous attacks of rheumatic fever, as well as the presence of chronic valvular changes from preceding attacks. This has enabled them to study the pathologic changes in the lung in relation to the acuteness and the duration of the rheumatic fever.

Forty-five cases of acute rheumatic heart disease were studied at autopsy and were divided into three groups on the following basis: (1) absence of previous history of rheumatic fever, no evidence of chronic valvular disease and an acute, rapidly fatal initial attack, (2) a previous history of rheumatic fever, evidence of chronic valvular disease and a rapidly fatal course in the last admission, and (3) chronic rheumatic cardiovalvular disease with the fatal attack lasting a considerable time.

The following conclusions were drawn. A specific rheumatic lung or rheumatic pneumonia cannot be considered to exist. Aschoff bodies were not found in a single instance. A characteristic, though not specific, pulmonary picture is present, which consists of alveolitis, marked congestion, edema, engorgement, and the formation of hyaline membranes. These lesions are considered to be a result of damage to the capillaries, with resultant alterations in vascular permeability. Vascular damage was likewise present in the main pulmonary artery and its branches and in the hepatic capillaries. This vascular change corresponds to the involvement seen in the arterial tree in various organs of the body in acute rheumatic fever.

AUTHORS.

Glazebrook, A. J., and Thomson, S.: *The Pulse Rate in Acute Juvenile Rheumatism*. Edinburgh M. J. 68: 619, 1941.

A pulse depression was found to be a common feature of the first attack of rheumatism in adolescents and young men. It occurred at an early stage and was often of a transient nature. Its recognition may aid diagnosis. It appeared to afford an index of the severity of the toxemia. It was associated with a marked sinus arrhythmia and sometimes progressed into a temporary partial heart block. A similar depression was seen in streptococcal infections which are possibly closely allied to the rheumatic state. The prognostic significance of a pulse depression as regards permanent cardiac damage was considered to be bad.

AUTHORS.

Page, I. H.: *The Nature of Clinical and Experimental Arterial Hypertension (the Edward Gamaliel Janeway Lecture)*. J. Mt. Sinai Hosp. 8: 3, 1941.

The development of knowledge of experimental hypertension, the relation of hypertension to vascular changes in the kidney, and the present conception of clinical hypertension are reviewed. The action of renin and angiotonin is described, and the evidence for the existence of a pressor-inhibition and its usefulness in the treatment of essential and malignant hypertension is presented.

MCCULLOCH.

Naide, M.: *The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans*. Am. J. M. Sc. 202: 822, 1941.

A study has been made of patients with thromboangiitis obliterans with regard to the possibility that the disease may be caused or precipitated by fungi which cause dermatophytosis. While evidence has been presented suggesting an etiological relationship between the two diseases, it is insufficient, at present, to be

conclusive. Nevertheless, certain clinical features of thromboangiitis obliterans are more readily accounted for on the basis of fungous infection than by other etiological agents thus far proposed. It therefore seems of primary importance to look for and to treat persistently any evidence of dermatophytosis in the patient with thromboangiitis obliterans.

AUTHOR.

Davies, D. H.: Idiopathic Cystic Medial Necrosis of the Aorta. *Brit. Heart J.* 3: 166, 1941.

A case of idiopathic cystic medial necrosis of the aorta, without rupture, has been reported. The presenting signs were those of aneurysmal dilatation of the aorta with aortic incompetence and terminal left ventricular failure.

AUTHOR.

Mason, J. M.: The Treatment of Vascular Injuries. *Ann. Surg.* 114: 191, 1941.

The treatment of vascular injuries is discussed under the following headings:

1. The great improvement in the treatment of shock and hemorrhage brought about by developments in transfusion since the World War.
2. Classification of vascular injuries in regard to treatment:
  - a. Those which demand immediate treatment.
  - b. Those in which a brief period of delay is permissible.
  - c. Those which come under observation at a late period.
3. Dangers inherent to ligation of arteries, especially in patients already exsanguinated.
4. Measures for increasing the safety of ligations.
5. Traumatic aneurysms and arteriovenous communications.
6. Wounds of the heart.
7. Vascular injuries in the current war.
8. Experience in civil practice.

AUTHOR.

Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? *New England J. Med.* 225: 433, 1941.

Clinically, there are characteristic syndromes that correspond to the diagnostic terms of scleroderma, dermatomyositis, disseminated lupus erythematosus, and polyarteritis nodosa. Not infrequently, however, patients present symptoms and signs that form essential characteristics of two or more of these conditions.

Since the diagnosis is almost always a clinical one without laboratory confirmation, the placing of undue emphasis on certain features may lead to diagnostic errors and a tendency to identify one disease with another.

There is no uniformity of opinion regarding the specific and fundamental pathology of certain of these syndromes, all of which represent a widespread vascular involvement, differing usually in the extent of the pathologic change, the size of the vessels involved, and the organs chiefly affected.

AUTHOR.

Takats, G. de: Management of Peripheral Vascular Disease. *Illinois M. J.* 80: 307, 1941.

A simple classification of peripheral vascular disease is presented by grouping vascular occlusions into acute, chronic, organic, functional, inflammatory, degen-

erative, vasospastic, and vasoparalytic occlusions. The purpose of an examination of the peripheral vascular status is to determine these various elements in the individual case and to estimate the capacity of the vascular bed. The objectives of treatment have been summarized under three headings, namely, the improvement of collateral circulation, the alleviation of pain, and the removal of nonviable parts in the optimal time and level. Methods of treatment are discussed under physical, medical, and surgical methods. An intelligent coordination of these procedures will yield the best results. The use of heat should be limited to the root of the limb, and the affected limb should be wrapped in cotton and kept at room temperature. Alternate hot and cold baths have not been used, but warm sitz-baths are recommended. Postural exercises, massage, and diathermy are discussed briefly. The use of sodium chloride by iontophoresis has given encouraging results in softening of sclerodermic and thrombophlebitic indurations. Alternate suction and pressure therapy has been given a thorough trial on ambulatory patients, and it was found that the degree of involvement present at the onset of the treatment determines the benefit one may expect from such therapy. Intermittent venous hyperemia has been used to a great extent; many patients used it at home for several months and years. The mechanical filling and stretching of the vascular tree undoubtedly helps to develop a collateral circulation. The author has not been able to find any difference between the clinical results obtained by this method and the suction and pressure treatment.

The object of drug therapy in peripheral vascular disease is to dilate the peripheral vascular bed. This can be obtained by measures producing central vasodilation through fever or by direct action on the smooth muscles of the blood vessels. Typhoid vaccine has been used to a great extent, but fever- or chill-producing doses have been avoided and only subreactionary doses have been given. Only patients with inflammatory lesions have been given typhoid vaccine. Hypertonic solutions have not been used, but sodium chloride can be given by mouth in 10 to 15 gr. tablets. Diets low in potassium accomplish the same effect. Alcohol is permitted and encouraged for those who are accustomed to taking it in moderate doses. Abstinence from tobacco is insisted upon in Buerger's disease and less rigidly enforced in arteriosclerotic patients. Theocalcin is used in the arteriosclerotic group because of its favorable action on impaired coronary circulation. Its effect on the peripheral vascular bed is doubtful when given in the customary doses by mouth. Papaverine is used in  $\frac{1}{2}$  gr. doses and is given intravenously in early cases of embolism and acute thrombosis. Nitrites and choline derivatives have been used extensively. Iodides, given intermittently to arteriosclerotic patients and to patients with Buerger's disease, are still being continued mainly on an empirical basis.

The indications for sympathectomy in peripheral circulatory disturbances have been summarized. The causes of failure, which are so often emphasized, are readily found in incomplete operations and improper selection of cases. The properly selected case derives great benefit from this operation. The use of paravertebral block with procaine in acute vascular occlusion and the indications for paravertebral block with alcohol are discussed. A peripheral nerve block in the presence of continuous intractable pain has a small but important part in the treatment of peripheral vascular disorders. When parts of the extremity are irrevocably lost or endanger life by absorption or spreading infection, amputation should not be delayed. The proper level of amputation must be determined by the level of adequate circulation and in consideration of adequate weight bearing. The technique of amputations today is such that these are now delicate, plastic operations performed under low spinal anesthesia and with a low mortality. The rehabilitation of amputated patients should and can be successfully undertaken.

AUTHOR.

Ravdin, I. S., and Wood, F. C.: The Successful Removal of a Saddle Embolus of the Aorta, Eleven Days After Acute Coronary Occlusion. *Ann. Surg.* 114: 834, 1941.

A physician, aged 32 years, suddenly developed symptoms and signs which led to the clinical diagnosis of cardiac infarction in the anterior surface of the left ventricle. While at rest in the hospital on the eleventh day, he awoke with an agonizing pain in both legs with coldness and mottling. He himself made a correct diagnosis of an embolus at the bifurcation of the aorta. At the operation the embolus was removed successfully. The patient made an uneventful recovery and is well after more than a year.

Immediately after the embolectomy, novocain was injected into the left paravertebral sympathetic plexus for nerve block to relieve vascular spasm distal to the arterial obstruction. Heparin also was given for eleven days following operation to prevent distal propagation of a thrombus.

The author believes that embolectomy is not always necessary in major arterial obstruction. The decision depends on whether or not there is evidence of continuing improvement in circulation. If this fails to occur, operation should be carried out, for, after three to five hours, changes in the intima at the site of the occlusion may result in further thrombosis, despite the use of heparin, following the closure of a vessel.

McCULLOCH.

Payne, R. T.: The Scope of Operation in Treatment of Varicose Veins. *Brit. M. J.* 2: 533, 1941.

The adequate treatment of primary uncomplicated varicose veins involves the complete obliteration of the varicose circulation.

Injection treatment will secure this in most cases; but operation, or more often a combination of operation and subsequent injections, is necessary for some cases, particularly the more advanced ones.

No case is too severe for the combined treatment.

The absolute and relative indications for operative treatment are given.

The details of preoperative treatment, operation, and postoperative care are described, and subsequent injection treatment is outlined.

The whole varicose circulation can be obliterated completely in six to eight weeks from the time of operation, and the patient rendered fit even for heavy work.

Patients with the severe type of varicosity should be examined at intervals of one year whenever possible.

The factors governing prognosis are outlined. Of the controllable factors, the most important is the completeness of the obliteration of the varicose circulation.

AUTHOR.

Ciocco, A., Klein, H., and Palmer, C. E.: Child Health and the Selective Service Physical Standards. *Pub. Health Rep.* 56: 2365, 1941.

The main purpose of this inquiry was to determine whether in childhood there were appreciable indications of the defects that have brought about the present disqualification of selectees. For this purpose an attempt has been made to compare, for each disqualifying cause, the childhood status of men who were rejected because of this cause with that of men who successfully passed the physical examination.

Twenty-seven selectees were disqualified because of some impairment of the cardiovascular system; records of school physical examinations and medical histories were available for twenty. At the time of the school examination some form of cardiac

abnormality was recorded for seven, or about one-third of the twenty men. Loud murmurs were noted for three, including one whose heart was said to be enlarged. A fourth was alleged to have "heart disease"—without further elucidation—and tachycardia was reported for a fifth. There was a history of rheumatic fever for two other selectees. Among the 149 selectees in Class 1-A for whom childhood physical examination records are available, none was stated to have any involvement of the cardiovascular system at the time of the school examination.

Since the study deals with a relatively small sample, perhaps too much weight should not be attached to the fact that seven of twenty young adults rejected for heart disease had, as children, some manifestation of rheumatic fever or cardiac symptom at the examination made in school, while no such sign was observed at the corresponding examination of the present-day selectees of Class 1-A. However, it must be recalled that, as is usually the case in school examinations, none of the records is sufficiently descriptive to give detailed information regarding the actual status of the heart muscle and function at the time.

AUTHORS.

White, P. D.: *The Soldier and His Heart*. War Med. 1: 158, 1941.

The author discusses briefly the problems relating to the heart which confront the draftee and the examining and classifying boards. In an appendix he gives the regulations concerning the heart, blood vessels, and the circulation from the standards of a physician's examination during the mobilization issued by the War Department in 1940.

McCULLOCH.

Master, A. M.: *Effort, Trauma, Occupation and Compensation in Heart Disease*. Bull. New York Acad. Med. 17: 778, 1941.

The relation of effort, occupation, and trauma to heart disease frequently offers a difficult problem, and each case must be carefully considered.

Symptoms may be due to pre-existing heart disease and the effort or trauma coincidental. Yet effort and trauma may aggravate previous heart disease. Effort does not damage a normal heart.

The effort is significant if it is unusual and not routine, and if symptoms arise immediately or soon after. The latter is also true of trauma.

A "stroke" may occur in the course of hypertension and arteriosclerosis. It is probably not related to effort, but the effect of trauma cannot be excluded.

Heart failure usually is a result of progressive heart disease and may be induced by infection. Only rarely is it precipitated by exertion, but the latter may aggravate it.

Angina pectoris is associated with coronary sclerosis. Individual attacks may be related to effort or trauma but later attacks or a persistent anginal syndrome rarely is.

Effort, occupation, and trauma play no role in coronary occlusion. The opposite view is often based on a confusion of coronary occlusion with the syndrome of angina pectoris, preliminary pain in coronary occlusion, and contusion of the heart.

Coronary insufficiency usually occurs in association with coronary sclerosis and may be related to effort and trauma.

Rheumatic fever rarely if ever is precipitated by effort or trauma.

Aortic aneurysm due to syphilis or sclerosis is not produced by effort or trauma. In rare instances effort or trauma may lead to rupture or to dissecting aneurysm.

Trauma may produce commotio cordis and contusion of the heart. In addition, the heart, large vessels and, in very rare instances, a valve may be ruptured.

Trauma does not produce coronary occlusion, and it probably does not lead to a persistent anginal syndrome.

Trauma may be the result, and not the cause, of heart disease.

Subacute bacterial endocarditis is not causally related to trauma with infection, but acute bacterial endocarditis sometimes is.

• Cardiac irregularities may be induced by effort or trauma.

Carbon monoxide poisoning occasionally results in damage to the heart, or aggravates a pre-existing condition, but it does not lead to coronary occlusion. Most cases of cardiac involvement attributed to carbon monoxide are based on insufficient evidence.

While neurocirculatory asthenia usually occurs in persons constitutionally susceptible to strain, in rare instances the onset of symptoms may be related to effort or trauma.

The problem of compensation in heart disease would be simplified considerably if a completely trustworthy history could be obtained in every case.

AUTHOR.

**Battro, A., Segura, R. G., and Lanari, A.: The Action of Hypertensin in Normal and Hypertensive Subjects. *Rev. argent. de cardiol.* 8: 250, 1941.**

The intravenous injection of hypertensin (1 unit per 10 kg. weight) in fourteen normal and nine hypertensive subjects produced a rise in systolic (average 36.4 and 32.7 mg. Hg, respectively) and diastolic (average 31.7 and 26.6 mm. Hg, respectively) blood pressure lasting five to nine minutes. Previous injection of atropine increased and prolonged the pressor action of hypertensin. No changes occurred in the ventricular complex of the electrocardiogram.

The injection of hypertensin into the brachial artery was followed by a marked reduction of the oscillometric index which persisted for thirty minutes in one case.

No relation between sensitivity to the cold test and to the pressor action of hypertensin was found in hypertensive patients.

AUTHORS.



## Book Reviews

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CLINICAL ELECTROCARDIOGRAPHY: By David Scherf, M.D., and Linn J. Boyd, M.D., Associate Clinical Professor of Medicine, and Professor of Medicine, respectively, New York Medical College, Flower and Fifth Avenue Hospitals. The C. V. Mosby Co., St. Louis, 1941, second impression, 362 pages, 207 figures, \$7.50.

This brief work on electrocardiography is a satisfactory introduction to the subject. It serves a purpose in acquainting the beginner in this field with the fundamentals of electrocardiography. There are now a number of good works on electrocardiography, and each will occupy its own position. This book is not encyclopedic but does include the majority of the accepted interpretations. The work is predominantly continental in its viewpoint and is to be recommended.

HAROLD FEIL.

TRASTORNOS CARDIACOS EN LOS ESTADOS ANEMICOS: By Dr. Eugenio R. Pietrafesa, Libreria y Editorial "El Ateneo," Buenos Aires, 1941, 207 pages, 127 illustrations.

As indicated by the title, this book presents a clinical and experimental investigation of cardiac disturbances in anemic states. The author studied twenty cases of severe anemia in which there were signs and symptoms related to the heart and blood vessels. Heart murmurs, arterial and venous murmurs, anginal pain, changes in the size of the heart, and electrocardiographic abnormalities were investigated. Experimental attempts to reproduce the electrocardiographic changes shown by anemic patients are reported, and histologic sections of the heart muscle of the experimental animals are discussed.

The heart murmurs are explained as the result of either increased velocity of blood flow or functional insufficiency of valves caused by cardiectasis.

Anginal pain was present in only a small percentage of cases and is attributed to coronary insufficiency caused by low oxygen tension of the blood.

The heart was enlarged in all cases. This enlargement was reversible, and was due to dilatation of the ventricles. In some cases there was also dilatation of the pulmonary artery, and, in others, of the left auricle. These phenomena are attributed to the effects of coronary insufficiency on the heart muscle.

The electrocardiograms showed low voltage of QRS and of the T wave, downward displacement of the S-T segment in Leads I and II, and, less often, changes in the P wave. The author ascribes these abnormalities to coronary insufficiency caused by the anemia.

Dyspnea, palpitation, sinus tachycardia, extrasystoles, splitting of the second heart sound, gallop rhythm, and hypotension were observed; all of these disappeared when the condition of the blood improved.

The author discusses the question whether anemia may cause congestive heart failure, with or without angina pectoris, as some have maintained. Four of his patients had congestive failure and recovered completely when their anemia was treated with iron or liver. Digitalis had no effect in these cases.

The experimental work was done on rabbits. They were bled repeatedly and exercised. Their electrocardiograms showed changes which were similar to those encountered in patients with severe, chronic anemia, and this tended to substantiate the idea that coronary insufficiency is the cause of these changes.

The book is well written and well printed. The author cites many previous studies, and it is sometimes difficult to separate his data from those of others. Detailed clinical reports and three indexes are included.

ALDO LUISADA.

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### Erratum

In the March issue of the JOURNAL, page 333, Dr. Miller's discussion of the article "The Induced Anoxemia Test" by Clough Turrill Burnett, M.D., Marshall Grant Nims, M.D., and C. J. Josephson, M.D., should read:

DR. H. R. MILLER, New York, N. Y.—Dr. Burnett's excellent studies raise the question—and I hope Dr. Burnett will comment on this—whether, in subjecting the normal subject to a lowered arterial oxygen saturation, we are dealing with an effect of deprivation of oxygen of central autonomic nuclear masses, or of the heart, or perhaps with both factors. The reactions noted by Dr. Burnett would seem to indicate that central autonomic controls of the cardiovascular apparatus were involved. It is now recognized by physiologists that various levels of the brain have an optimal reaction in accordance with the quantity of oxygen made available for their utilization.

The second point I have in mind is the matter of syncope in association with cardiovascular states. It is a commonplace that, when there is cardiovascular depression, syncope is very likely to occur, but syncope may also occur without cardiovascular depression. Stimulation of certain areas of the brain may produce marked signs of cardiovascular depression, but no syncope. On the other hand, stimulation of such a trigger zone as the carotid sinus area is known to cause marked circulatory depression, often with syncope, but, at times, without this depression. These results, it seems to me, direct our attention to an interesting point. Is there a separate mechanism responsible for syncope? In other words, when syncope takes place as a result of either central or peripheral excitation or inhibition, and in the absence of cardiovascular features, are we dealing with a mechanism which is independent of the autonomic regulation of circulation?

In the kind of test studied by Dr. Burnett and his co-workers the normal subject may be reacting primarily by virtue of some change in his heart muscle, or the cardiac effect may be only a localized expression of a much more extensive autonomic effect. If we, as clinicians, are to employ a test of this character, we must be certain that the effect is chiefly and primarily on the heart, and not widespread and generalized.

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A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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\*Executive Committee.

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## Original Communications

### THE CLINICAL FEATURES OF TRICUSPID STENOSIS

#### A STUDY OF TRIVALVULAR STENOSIS

JASPER A. SMITH, M.D., AND SAMUEL A. LEVINE, M.D.  
BOSTON, MASS.

THE accuracy of diagnosis of valvular disease has improved greatly in recent years. The introduction of electrocardiography, although contributing mainly to our knowledge of coronary artery and myocardial disease, has indirectly aided in the diagnosis of valvular disease. The presence of right or left axis deviation has occasionally been the clue that has led to the recognition of a valvular lesion that otherwise might have been overlooked. The peculiar form of the P wave in some cases of mitral stenosis at times serves to identify this lesion when other methods leave one in doubt. The greater interest that has been taken in x-ray examination of the heart has also thrown considerable light on the diagnosis of valvular disease. Not only the correlation between the configuration of the cardiac silhouette and the post-mortem findings, but also fluoroscopic examinations have established certain general patterns that more or less correspond to specific types of valvular disease. Of even greater roentgenologic importance is the detection of calcification of the valves of the heart by fluoroscopic examination.<sup>1</sup> Apart from all of this, bedside methods of inspection, palpation, auscultation, and percussion have become more precise. The result has been that a well-trained clinician is able to make a fairly accurate diagnosis of the anatomic condition of the valves in most cases.

Mitral stenosis, the most important of the valvular defects, is also the defect diagnosed most accurately. Aortic valvular disease, particularly aortic stenosis, has only recently been recognized as a common lesion, and methods of its detection are becoming more clearly understood. It is still too frequently overlooked, but at present it is fair to

From the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Medicine of the Harvard Medical School, Boston.  
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TABLE I

| CASE NO.                           | AGE AT DEATH (YEARS) | SEX | DURATION OF RHEUMATIC HISTORY (YEARS) | DURATION OF FAILURE (YEARS) | HEPATIC ENLARGEMENT* | RHYTHM    | AXIS DEV. | P-WAVE CHANGES       | TRICUSPID STENO-SIS* | MITRAL STENO-SIS* | AORTIC STENO-SIS* |
|------------------------------------|----------------------|-----|---------------------------------------|-----------------------------|----------------------|-----------|-----------|----------------------|----------------------|-------------------|-------------------|
| <i>Marked Tricuspid Stenosis</i>   |                      |     |                                       |                             |                      |           |           |                      |                      |                   |                   |
| 1                                  | 40                   | F   | 31                                    | 23.0                        | 3                    | A.F.      | R.A.D.    | A.F.                 | 3                    | 3                 | 0                 |
| 2                                  | 36                   | F   | 30                                    | 3.5                         | 0                    | Flutter   | R.A.D.    | Flutter              | 3                    | 3                 | 1                 |
| 3                                  | 39                   | F   | 25                                    | 7.0                         | 1                    | A.F.      | R.A.D.    | A.F.                 | 3                    | 3                 | 2                 |
| 4                                  | 20                   | F   | 17                                    | 0.2                         | 3                    | Reg.      | R.A.D.    | Broad, flat          | 3                    | 3                 | 2                 |
| 5                                  | 45                   | F   | 36                                    | 3.0                         | 3                    | A.F.      | R.A.D.    | A.F.                 | 3                    | 3                 | 3                 |
| 6                                  | 32                   | F   | 11                                    | 5.5                         | 3                    | Reg.—A.F. | R.A.D.    | Broad, flat, notched | 3                    | 3                 | 3                 |
| 7                                  | 17                   | F   | 9                                     | 0.5                         | 3                    | Reg.      | ?         | ?                    | 3                    | 3                 | 2                 |
| 8                                  | 21                   | F   | 12                                    | 3.5                         | 3                    | A.F.      | R.A.D.    | A.F.                 | 3                    | 3                 | 2                 |
| 9                                  | 27                   | F   | 9                                     | 2.5                         | 1                    | Reg.      | ?         | ?                    | 3                    | 3                 | 2                 |
| 10                                 | 45                   | F   | 30                                    | 8.0                         | 3                    | A.F.      | ?         | ?                    | 3                    | 3                 | 3                 |
| 11                                 | 36                   | F   | ?                                     | 15.0                        | 3                    | A.F.      | R.A.D.    | A.F.                 | 3                    | 3                 | 3                 |
| Av.                                | 32.5                 |     | 21.0                                  | 6.5                         | 2.4                  |           |           |                      | 3.0                  | 3.0               | 2.1               |
| <i>Moderate Tricuspid Stenosis</i> |                      |     |                                       |                             |                      |           |           |                      |                      |                   |                   |
| 12                                 | 38                   | F   | 19                                    | 12.0                        | 0                    | Reg.      | None      | Low, broad, flat     | 2                    | 2                 | 2                 |
| 13                                 | 43                   | F   | 10                                    | 8.0                         | 3                    | A.F.      | R.A.D.    | A.F.                 | 2                    | 3                 | 0                 |
| 14                                 | 24                   | M   | 14                                    | 20.0                        | 2                    | Reg.      | R.A.D.    | Small, flat, notched | 2                    | 3                 | 1                 |
| 15                                 | 23                   | M   | 10                                    | 1.5                         | 3                    | Reg.      | R.A.D.    | Coarsely notched     | 2                    | 3                 | 2                 |
| 16                                 | 43                   | F   | 29                                    | 1.0                         | 3                    | A.F.      | R.A.D.    | A.F.                 | 2                    | 3                 | 3                 |
| 17                                 | 51                   | F   | 43                                    | 4.0                         | 1                    | A.F.      | None      | A.F.                 | 2                    | 3                 | 3                 |
| 18                                 | 44                   | M   | 21                                    | 18.0                        | 2                    | A.F.      | R.A.D.    | A.F.                 | 2                    | 3                 | 3                 |
| 19                                 | 27                   | F   | 15                                    | 10.0                        | 2                    | Reg.      | ?         | ?                    | 2                    | 3                 | 2                 |
| 20                                 | 39                   | F   | 17                                    | 10.0                        | 3                    | A.F.      | R.A.D.    | A.F.                 | 2                    | 3                 | 1                 |
| 21                                 | 18                   | M   | 10                                    | 4.0                         | 3                    | Reg.—A.F. | ?         | ?                    | 2                    | 3                 | 0                 |
| 22                                 | 38                   | F   | 30                                    | 3.0                         | 1                    | Reg.      | ?         | ?                    | 2                    | 3                 | 2                 |
| Av.                                | 35.2                 |     | 19.8                                  | 8.3                         | 2.1                  |           |           |                      | 2.0                  | 2.9               | 1.7               |

| <i>Slight Tricuspid Stenosis</i> |      |   |      |      |     |           |        |                      |     |     |     |  |
|----------------------------------|------|---|------|------|-----|-----------|--------|----------------------|-----|-----|-----|--|
| 23                               | 32   | M | 10   | 0.3  | 3   | Reg.      | L.A.D. | Broad, flat, notched | 1   | 2   | 0   |  |
| 24                               | 38   | M | 20   | 0.5  | 0   | Reg.      | R.A.D. | Flat top, notched    | 1   | 2   | 0   |  |
| 25                               | 39   | F | 30   | 19.0 | 2   | A.F.      | R.A.D. | A.F.                 | 1   | 2   | 0   |  |
| 26                               | 47   | F | 24   | 14.0 | 3   | Reg.      | None   | Broad, flat, notched | 1   | 2   | 2   |  |
| 27                               | 51   | F | 47   | 15.0 | 3   | A.F.      | R.A.D. | A.F.                 | 1   | 2   | 2   |  |
| 28                               | 26   | F | 16   | 16.0 | 3   | Flutter   | R.A.D. | Flutter              | 1   | 3   | 0   |  |
| 29                               | 27   | M | 7    | 0.0  | 3   | A.F.      | R.A.D. | A.F.                 | 1   | 3   | 0   |  |
| 30                               | 48   | M | 30   | 1.5  | 2   | Reg.      | R.A.D. | Sharp, notched       | 1   | 3   | 1   |  |
| 31                               | 26   | M | 5    | 1.5  | 3   | Reg.—A.F. | R.A.D. | Broad, flat, notched | 1   | 3   | 2   |  |
| 32                               | 24   | F | 21   | 5.0  | 1   | Reg.      | R.A.D. | Broad, flat, notched | 1   | 3   | 3   |  |
| Av.                              | 35.8 |   | 21.0 | 8.1  | 2.3 |           |        |                      | 1.0 | 2.5 | 1.0 |  |
| <i>Entire Group (32 Cases)</i>   |      |   |      |      |     |           |        |                      |     |     |     |  |
| Av.                              | 34.3 |   | 20.8 | 7.4  | 2.3 |           |        |                      | 2.0 | 2.8 | 1.6 |  |

\*1 = slight; 2 = moderate; 3 = marked.

say that, unless the patient is moribund, aortic stenosis can be recognized in the majority of cases. The lesion that has so far defied clinical recognition is organic tricuspid valvular disease, either stenosis or insufficiency. That organic involvement of this valve is by no means rare will become clear from the results of this present study. We are aware of no published communication which indicates that the antemortem diagnosis of tricuspid valvular disease is being made with any degree of accuracy comparable to that which obtains in the diagnosis of aortic or mitral disease. In fact, the experience has been that most cases of tricuspid stenosis are first recognized at the autopsy table.

There is at present no satisfactory sign or symptom that characterizes organic tricuspid disease. The systolic pulsation of the veins in the neck, or even of the liver, has long been recognized as evidence of incompetency and regurgitation of the tricuspid valve. Tricuspid insufficiency, however, not infrequently results when the heart is dilated and the tricuspid valve is relatively incompetent whether organic valvular disease is present or not. In other words, tricuspid insufficiency is not synonymous with tricuspid endocarditis. An elevated venous pressure, although common, if not invariable, in tricuspid stenosis, is present whenever there is right-sided failure or venous obstruction of the heart irrespective of the underlying cause. Large, distended jugular or temporal veins, although suggestive of tricuspid involvement, may be present without this lesion. Systolic pulsations of the liver have often been looked upon as evidence of tricuspid disease, but at times it is difficult to elicit this sign, as the movements of the liver may be due to direct impact from the adjacent aorta or heart. It is of more value when, on bimanual palpation, the liver can be actually felt to expand so that simultaneously a forward movement may be made out with one hand and a backward movement with the other. This merely indicates that there is tricuspid insufficiency. There have been occasions when prominent auricular waves could be detected in polygraphic tracings taken in the region of the liver. Likewise prominent auricular waves in jugular tracings have been described as occurring in tricuspid stenosis.

Little progress has been made in the interpretation of murmurs that might identify this lesion. One would expect to find systolic or diastolic murmurs in the tricuspid area, just as similar murmurs are heard at the apex in the case of mitral stenosis. The difficulty is that practically all cases of tricuspid stenosis have accompanying mitral stenosis, and many have aortic stenosis as well. Because the mitral and tricuspid valves are situated in close proximity, and the resultant murmurs can be of the same time and character, interpretation of auscultatory findings will always be difficult and confusing. Some of the older clinicians have called attention to the peculiar olive discoloration of the skin associated with tricuspid disease. One would predict that, just as the left auricle dilates with mitral stenosis, the right would dilate with

tricuspid stenosis. This evidence ought to be detectable on x-ray examination. Finally, the only information which electrocardiography could possibly furnish that might directly result from the tricuspid lesion would be evidence of right auricular dilatation and hypertrophy. Right axis deviation, if present, results from the mitral stenosis that coexists, for the right ventricle becomes enlarged not from the tricuspid, but from the mitral stenosis. Other clinical findings, such as undue cyanosis and polycythemia, have been thought to accompany tricuspid disease, but the fact that the diagnosis is rarely made with accuracy is sufficient evidence that none of the above criteria are diagnostically reliable. This study was therefore undertaken with the purpose of throwing some light on the diagnostic criteria and the clinical features that might aid in the recognition of organic tricuspid valvular disease.

The records of the pathologic department of the Peter Bent Brigham Hospital from 1913 to 1940 inclusive were analyzed. In a total of 4,437 autopsies 340 cases of rheumatic valvular disease, i.e., an incidence of 7.7 per cent, and 227 cases of mitral stenosis were found. Among these there were thirty-two cases of definite tricuspid stenosis, i.e., 9.4 per cent of all chronic rheumatic valvular disease. The degree of stenosis was regarded as marked in eleven, moderate in eleven, and slight in ten cases (Table I). Every case had an associated mitral stenosis. In addition there were sixty cases in which the tricuspid valve showed definite evidence of structural organic involvement (17.6 per cent of all chronic rheumatic valvular disease), most of which had a functional insufficiency of the tricuspid valve; some may have had a slight degree of stenosis, but not sufficient to be certain. If both groups are considered, it is apparent that 27.0 per cent of all cases of chronic rheumatic valvular disease have some form of tricuspid involvement. Organic tricuspid disease, stenosis or insufficiency, therefore, cannot be a rare condition.

#### CLINICAL CONSIDERATIONS

The average age at the time of death for the entire group of thirty-two cases was 34.3 years. There were nine males and twenty-three females. The preponderance of females is in accord with similar findings in cases with mitral stenosis in general.<sup>2</sup> It is of interest that there were no males in the cases of marked tricuspid stenosis.

There was a history of rheumatic fever or chorea in twenty-five of the thirty-two cases (78 per cent). Fifteen had rheumatic fever without chorea, and two had chorea without rheumatic fever; the remaining eight had both. There were seven that had neither rheumatic fever nor chorea. Many of the patients had more than one attack of rheumatic infection. Recurrences of such attacks, however, had no influence on the severity of the valvular lesion. In fact, the reverse seemed to be true, inasmuch as the incidence of frequent bouts of rheumatic fever



or chorea was much greater in those with slight tricuspid stenosis than in those with a higher degree of stenosis. Although scarlet fever is related to valvular disease only in so far as it may initiate an attack of rheumatic fever, it is of interest that six of the patients had a past history of scarlet fever; three of these had an additional history of rheumatic infection. The interval that elapsed between the first rheumatic infection and death averaged 20.6 years. There was no difference in this interval when the various degrees of tricuspid stenosis were compared.

The Wassermann reaction was positive in only one case, and in that instance there was both syphilitic disease of the aorta and rheumatic disease of the valves. The average blood pressure of these cases was 121/74 mm. and showed no appreciable variation in the three different degrees of stenosis of the tricuspid valve. Significant hypertension was infrequent in the entire group, for there were only two cases in which the systolic pressure was over 150 mm. (160 and 165), and three others with diastolic readings between 100 and 110 mm. in which the systolic pressures were below 140 mm.

The duration of congestive failure was an important part of this investigation because our original concept was that tricuspid stenosis seemed to protect the pulmonary circuit and delay the development of pulmonary congestion, that otherwise may progress rapidly in cases of mitral stenosis. When the cases in this study were analyzed from this point of view, it was found that the average duration of life after the first appearance of congestive heart failure (enlarged liver, ascites, pitting edema, basal râles or significant breathlessness) was 7.4 years. As has been shown in a previous communication,<sup>3</sup> this is considerably longer than for cases of pure aortic stenosis, pure mitral stenosis and combined aortic and mitral stenosis. In that study the duration of congestive failure was found to be 1.4 years in pure aortic stenosis, 2.9 years in pure mitral stenosis and 3.5 years in combined aortic and mitral stenosis. Further analysis showed that the duration was distinctly longer for those with moderate than those with marked tricuspid stenosis (8.3 and 6.5 years, respectively). The effect of aortic or mitral involvement in these cases of tricuspid stenosis was also investigated. In the twenty-four cases with some degree of aortic stenosis the duration of symptoms was 6.5 years, while in the eight without aortic involvement it was 8.4 years. Similar figures for the twenty-six cases of marked mitral stenosis and the six with only moderate mitral stenosis were 6.7 years and 10.1 years, respectively. It follows from the preceding analysis that aortic stenosis and mitral stenosis both tend to shorten, while tricuspid stenosis tends to lengthen, the duration of life after the onset of congestive failure.

Peripheral edema is common in all types of congestive heart failure and especially in cases of tricuspid stenosis. This is not invariably true,

for six of this series had no significant pitting edema. This may or may not have been the result of effective diuretic therapy. A subicteric tint of the skin is a frequent finding in tricuspid stenosis, but in this study it did not seem to be related to the severity of tricuspid stenosis. Cyanosis in tricuspid stenosis appeared to be more prominent than in other types of cardiac decompensation with the possible exception of chronic cor pulmonale. It also had a tendency to persist to some extent even when the patient had improved and was ambulatory. As pointed out by Altshule and Budnitz,<sup>4</sup> this cyanosis can be looked upon as a result of distention and engorgement of the peripheral veins and venules, and not as a result of a lowered oxygen content of the venous or arterial blood. Ascites occurred in slightly more than one-third of the cases and was distinctly more common in marked stenosis. In fact, ascites, requiring frequent abdominal paracentesis, is a conspicuous feature in some cases of tricuspid stenosis, resembling pericardial constriction in this respect. The presence of orthopnea proved difficult to appraise, for, as the condition progressed, it almost always developed. During the earlier stages, however, even when the liver was enlarged and ascites was present, orthopnea was often absent or negligible. Abdominal pain in the region of the liver was a frequent complaint, occurring in two-thirds of the cases, and was more marked in those with a higher degree of tricuspid stenosis. Although the liver was usually palpable (all but three cases), it appeared to be larger clinically than its actual post-mortem weight would indicate. In several instances definite liver expansile pulsations could be elicited.

Pulsation of the jugular veins is expected to be present in most cases of tricuspid disease. It will obviously be more prominent when there is a greater degree of tricuspid regurgitation and less stenosis. This proved to be the case, as it was much more frequent and more prominent in those with slight than in those with marked tricuspid stenosis. With these pulsations the veins were practically always found to be well distended. One characteristic feature of this distention was that it was apt to persist even when the patient had improved and had become ambulatory.<sup>5</sup> Determinations of venous pressure in the arm were made in only three instances. These readings were 300 mm., 340 mm., and 250 mm. of water. The changes in pressure were not followed with the cycles of improvement, but it is surmised that the pressure remains permanently elevated in all cases with appreciably stenosed tricuspid valves.

Auricular fibrillation was present in eighteen of the thirty-two cases. The average age at death for this group was 39 years and the average of the fourteen with regular rhythm was 29 years. This discrepancy cannot be explained on any difference in the degree of stenosis of the various valves, for there was more stenosis in the fibrillators than in the nonfibrillators. The average age at which the first rheumatic infection

occurred was identical in the two groups (i.e., fourteen years), and the duration of life from this first rheumatic infection was twenty-five years in the fibrillators and fifteen years in the nonfibrillators. A possible explanation of this discrepancy is that the proportion of patients who died of the complications of heart disease (rather than in pure failure) in the nonfibrillating group was greater than in the fibrillating group. If complications such as embolism and infection do not occur while the rhythm is regular, the patient may live on for many years, develop fibrillation, and then die of either heart failure or one of the complications.

There seemed to be a suggestive relationship between the relative size of the two auricles and the presence of auricular fibrillation. It is of interest that, of the seven cases in which the left and right auricle were judged to be of equal size, six had a regular rhythm and the other developed fibrillation not long before death. In the nineteen instances in which the right auricle was larger than the left, five were regular and fourteen were fibrillating. Three of the six cases in which the left auricle was larger than the right had a regular rhythm, and the other three had fibrillation. It would appear that an inequality in the size of the two auricles was an important factor in the development of auricular fibrillation.

The pulmonary second sound is accentuated in practically all cases of tricuspid stenosis, and this is to be accounted for by the invariable presence of mitral stenosis. One might surmise that the accentuation of  $P_2$  would be greater when mitral stenosis is unaccompanied by tricuspid stenosis. An analysis of the murmurs that were present was extremely difficult because systolic and diastolic murmurs heard at the apex were frequently also detected to the left of the lower sternum, and it was impossible to distinguish whether the mitral or the tricuspid valve, or both, were the origin of such murmurs. In some cases it appeared that the murmurs near the sternum had a slightly louder or different character than those near the apex. On physical examination the heart size was always found to be enlarged. In general, both the right and left border of dullness extended beyond the normal limits. The average percussion measurements for the entire group were 5.4 cm. to the right and 13.7 cm. to the left of the midline. X-ray examination was carried out in ten of these cases and confirmed the clinical impressions. Measurements from heart plates showed the following average figures: right border 5.8 cm. to the right, left border 11.9 cm. to the left, and internal diameter of the chest 25.3 cm. This indicates that cases of tricuspid stenosis show considerable increase in the size of the heart in both directions, but particularly to the right. After the pathologic observations of these hearts one can definitely say that the increased size of the heart is due mainly to dilatation of the two auricles,

as the ventricles are not particularly dilated and only moderately hypertrophied.

Pulmonary congestion as evidenced by basal râles or hydrothorax was eventually present in all but two cases. In some cases it was strikingly slight or absent for some years when there was already peripheral edema and an enlarged liver. The degree of pulmonary congestion was distinctly greater in cases with marked tricuspid stenosis. Polycythemia was not an impressive finding, as the average red blood count was 4.8 million, and the average hemoglobin, 91 per cent. There was only one case with a red blood count of over six million. In general, those with more marked congestive failure had a higher count, and one can say that the group as a whole was characterized by a high normal red blood count.

The four electrocardiographic findings that were studied were the cardiac rhythm, the voltage of the QRS complex, the degree of axis deviation, and the form of the P wave. Electrocardiograms were available in twenty-seven of the thirty-two cases in this study. Of these, thirteen consistently showed auricular fibrillation in all tracings that were taken. Ten always showed a regular rhythm. There were two that were at first regular and later developed fibrillation. One other showed first auricular flutter and then developed fibrillation, and the last constantly had auricular flutter. The remaining five cases in which electrocardiograms were not taken had a regular rhythm. Auricular fibrillation or flutter was present in slightly less than half of the entire series.

The QRS complex was regarded as being of low voltage (5 mm. or less) in seven cases; all seven showed moderate to marked edema. In two cases electrocardiograms were obtained at different periods, and they showed that the height of the QRS complex increased as edema disappeared.

A study of the electrical axis revealed that in three cases there was no axis deviation. This may possibly be explained by the fact that there was a considerable degree of aortic stenosis. Only one had left axis deviation, and in this instance there was an associated hypertension. The remaining twenty-three all showed varying degrees of right axis deviation. Two of the latter developed right axis deviation during the course of a year of observation. No correlation could be discovered between the severity of stenosis of the various valves and the degree of right axis deviation.

The form of the auricular complex, or P wave, was studied in twelve cases. All showed some of the changes that are associated with auricular hypertrophy or dilatation. These changes consisted of broadening at the base, increase in height, a flat top, and notching of the P wave. The cases varied in the degree of change, but all showed one or more of these abnormalities. The peculiarities of the P wave were somewhat

more prominent in Lead I than in Lead II. The electrocardiographic findings discussed above are those commonly regarded as accompanying mitral stenosis. What part may be attributed to the tricuspid stenosis present in this group remains in doubt. It would appear, however, that in the presence of a regular rhythm the absence of right axis deviation and the abnormal P waves previously mentioned would cast doubt on the diagnosis of tricuspid stenosis.

Total proteins and the serum albumin-globulin ratio were determined in only five instances. The average total protein was 5.8 Gm. per cent; serum albumin, 3.2 Gm. per cent; and the serum globulin, 2.6 Gm. per cent. The degree of edema and ascites was apparently in direct proportion to the lowering of the serum albumin level in the few cases studied. Analysis of one of these cases was particularly significant because frequent determinations were made during the course of the disease. On admission there was massive general anasarca and the total protein was 4.3 Gm. per cent; serum albumin, 2.2 Gm. per cent and serum globulin, 2.1 Gm. per cent. In the following five weeks, during which time the patient was taking a very high protein diet and receiving diuretics, there was a gradual loss of about 50 pounds of water. The total protein was 6.0 Gm. per cent; albumin, 3.7 Gm. per cent; and globulin, 2.3 Gm. per cent. At this time she was essentially edema-free. Three years later, shortly before death, the readings were: total protein 4.5 Gm. per cent, serum albumin 1.9 Gm. per cent, and serum globulin 3.6 Gm. per cent. During these intervening three years she kept her weight low and remained edema-free on weekly injections of mercupurin. This case illustrates the importance of a low serum albumin level in the mechanism of edema and ascites in cases of tricuspid stenosis.

#### AGE AT DEATH OF PATIENTS WITH TRICUSPID STENOSIS

The average age at death in thirty-two cases of tricuspid stenosis was 34.3 years. The oldest was 51 years and the youngest was 17 years at the time of death. The average age for those with marked tricuspid stenosis was 32.5 years; with moderate tricuspid stenosis, 35.2 years; and with slight tricuspid stenosis, 35.8 years. Although the difference is slight, patients with a high degree of tricuspid stenosis seem to succumb at a younger age.

#### EFFECT OF CONCOMITANT MITRAL STENOSIS

An attempt was made to study the effect of the accompanying mitral stenosis (which was always present) on the age of death. The degree of stenosis of all valves was indicated by the terms slight, moderate, and marked. There were no instances in which the mitral valve was only slightly stenosed, and all cases showed as great as or a higher degree of mitral stenosis than of tricuspid stenosis. When stenosis was equal

in extent in the two valves, it was practically always of marked degree and the age at death was 32.5 years. When the degree of stenosis was somewhat greater in the mitral than in the tricuspid (the reverse was never true), the average age at death was distinctly greater (37.1 years) than when the valves were equally stenosed (32.5 years). Even among these cases with unequal stenosis in the two valves, those with slight degree of constriction lived longest with an average of 41.4 years for five cases with slight tricuspid stenosis and moderate mitral stenosis as compared to 35.0 years for ten cases with moderate tricuspid stenosis and severe mitral stenosis. On the other hand, when the discrepancy in the degree of stenosis was greater, i.e., slight tricuspid stenosis with a marked mitral stenosis, the average age in five cases was low (30.2 years). The fact that the patients with severe mitral stenosis associated with moderate tricuspid stenosis die at an older age than those with severe mitral stenosis and slight tricuspid stenosis indicates that it is the tricuspid valve that influences the duration of life in these cases.\*

The obvious deduction that a greater degree of mechanical constriction of the mitral valve, apart from the condition of the tricuspid, indicates a graver condition is borne out by the finding that in twenty-six cases of marked mitral stenosis the average age at death was 33.0 years and in six cases of moderate mitral stenosis it was 40.8 years. One can conclude from the above analysis that, although mitral stenosis is the dominant lesion responsible for death, the time of death is determined by the accompanying tricuspid lesion and that, if the degree of stenosis of the latter is only slightly less than that of the former (i.e., moderate tricuspid stenosis and marked mitral stenosis), the maximum duration of life results.

Fatal cases with valvular disease can be arbitrarily divided into two groups, those dying with "pure" heart failure and those dying of complications. In the latter, death occurs from pulmonary infarction, peripheral emboli, intercurrent infections, subacute bacterial endocarditis, or any significant complication which terminates the natural progress of the disease prior to the final stage of fatal congestive failure. In the former, one may look upon the cardiac condition as having progressed to the advanced phase of irreversible congestive failure. When the thirty-two cases of tricuspid stenosis were divided into these two groups, we found that ten patients died with pure uncomplicated heart failure (all having marked mitral stenosis) at an average age of 31.2 years, while the other twenty-two patients in the second group died at an average age of 36.0 years. The reason for this paradoxical discrepancy is that the group with "pure failure" had a much higher degree of mitral and tricuspid stenosis and that the group dying of

\*It will be shown later that a marked degree of aortic stenosis is associated with a still greater age at death, but analysis of this specific group of cases indicated that the effect of the tricuspid valve on the duration of life is independent of the aortic factor.

"complications" had the optimum ratio in the degree of stenosis between the two valves, i.e., the tricuspid valve having one degree less stenosis than the mitral valve. It is of interest that none of the patients with only slight tricuspid stenosis died of pure failure. The progress of their disease was not permitted to run its entire span, being interrupted by one or another complication which proved fatal.

#### EFFECT OF CONCOMITANT AORTIC STENOSIS

Among these thirty-two cases of tricuspid stenosis, all of which had mitral stenosis as well, there were twenty-four, or 75 per cent, that had definite aortic stenosis. Aortic stenosis was marked in eight, moderate in twelve, and slight in four. The average age at death of those with severe aortic stenosis was 40.0 years; for the moderate and slight aortic stenosis, 32.6 years; and for those without aortic stenosis, 32.7 years. A similar but even greater discrepancy was found when marked aortic stenosis was compared to moderate aortic stenosis, each group having similar degrees of stenosis of the mitral and tricuspid valves. It was found that all cases of marked aortic stenosis had an associated degree of mitral stenosis that was of equal severity. In fact it may be stated from this study that when there is some stenosis of the tricuspid valve, if the aortic valve can be identified as being markedly stenosed, one may be fairly certain that the mitral valve will be markedly stenosed and the tricuspid at least moderately stenosed. It is evident that a high degree of aortic stenosis accompanying mitral and tricuspid stenosis is either conducive to, or concomitant with, a longer life expectancy than if a lesser degree of aortic involvement is present.

#### PATHOLOGIC CONSIDERATIONS

The average heart weight of the entire group was 506 Gm. (twenty-eight cases). Those with marked tricuspid stenosis had slightly heavier hearts. This figure seems much smaller than one might have expected from the large size of the heart and the great frequency of aortic stenosis. The explanation is that the large cardiac silhouette is due mainly to dilatation of the auricles, and the aortic stenosis does not continue for a great many years as it does in the pure aortic stenosis of older people, when it produces extreme hypertrophy of the left ventricle.

Estimates were made of the relative degree of enlargement of the right and left auricles from the description given in the autopsy protocols. All cases apparently had some enlargement of both auricles. The relative enlargement of the right auricle as compared to the left was decidedly greater in those with marked tricuspid stenosis than in those with lesser degrees of stenosis. The average thickness of the right ventricle was 5.5 mm. for the entire group, 6.1 mm. for those with marked tricuspid stenosis, and 5.1 for the remainder (normal about 4.0

mm.). When the group having slight tricuspid stenosis and marked mitral stenosis is compared with one having marked tricuspid stenosis and marked mitral stenosis, the average thickness of the former was found to be 7.0 mm. (five cases) and, of the latter, 6.1 mm. (nine cases). The inference follows that, whereas right ventricular hypertrophy results from mitral stenosis, an accompanying tricuspid stenosis tends to diminish the degree of right ventricular hypertrophy. Measurements of the left ventricle showed average figures of 16.0 mm. for the entire group, 18.0 mm. for those with marked tricuspid stenosis, and 14.7 mm. for the less stenosed cases (normal about 14.0 mm.). The greater thickness of the left ventricle in the cases of marked tricuspid stenosis was not due to the effect of the tricuspid valve, but to the greater incidence of marked aortic stenosis present in these cases. This is borne out by the figures for the relative thickness of the left ventricle in marked, moderate, and slight aortic stenosis which were 20.5 mm., 16.7 mm. and 16.0 mm., respectively. It was to be expected that the higher degrees of aortic stenosis would be accompanied by a thicker left ventricle.

The condition of the coronary arteries was investigated, and in only two was any significant degree of coronary sclerosis detected. Pericardial adhesions of greater or lesser extent were found in 42 per cent of the cases. This is a common finding in all types of rheumatic heart disease. Slight degrees of hydropericardium (less than 200 c.c.) were found in about a third of the cases, although in one case 1,000 c.c. of pericardial fluid were present.

Pulmonary infarctions were common, occurring in about half the cases. In general, peripheral arterial emboli occurred with about the same frequency as pulmonary infarction. The average weight of the liver showed interesting variations with different degrees of tricuspid stenosis. Whereas the average for the entire group was 1,535 Gm., the figures for marked, moderate, and slight tricuspid stenosis were 1,497, 1,393, and 1,755 Gm., respectively. Those with slight stenosis had the largest livers, probably because there were more congestion and less fibrosis in the liver.

Analysis was made of the accuracy of the clinical diagnosis of the various valve lesions. Mitral stenosis was recognized antemortem in every one of the thirty-two cases. Most of these also had an apical systolic murmur which could be considered indicative of concomitant mitral insufficiency. Of the twenty-four cases of aortic stenosis, thirteen were diagnosed definitely antemortem, and one was considered as having questionable aortic stenosis. In the other ten the presence of aortic stenosis was not recognized clinically. Moreover, it was thought to be present in four cases of the eight that did not have aortic stenosis. In other words, the accuracy of the diagnosis of presence or absence of aortic stenosis was slightly better than 50 per cent. A diastolic murmur



was heard either in the aortic area or along the upper left sternal border, which was interpreted as being due to an aortic insufficiency in sixteen of the thirty-two cases. Three of these were instances in which the presence of aortic stenosis was overlooked, but the finding of an aortic diastolic murmur at least enabled the clinician to incriminate the aortic valve as being involved. It is of interest that whenever aortic diastolic murmurs were heard (with two exceptions) there was pathologic evidence of aortic stenosis. The inference is that in cases with tricuspid stenosis, if one can diagnose aortic insufficiency, it is fairly safe to assume that aortic stenosis is present.

As was stated in the beginning of this paper, tricuspid stenosis has been, and still is, the most difficult of all common valvular lesions to diagnose. Only five of these thirty-two cases were regarded as having definite tricuspid stenosis antemortem, and one additional case as having questionable tricuspid stenosis. Even these figures do not tell quite the whole story, as different observers disagreed frequently in their diagnoses. Contrariwise, some of the cases that were overlooked would probably have been recognized if they had been examined by those especially trained in cardiovascular disease. During the past few years, because of increased interest in the recognition of tricuspid stenosis, greater diagnostic accuracy has been attained. This is shown by the fact that two of the last four cases of tricuspid stenosis were correctly diagnosed antemortem.\*

#### DISCUSSION

A study of tricuspid stenosis really consists of an analysis of tri-valvular stenosis, for it is clear from this review that all cases of tricuspid stenosis have an accompanying mitral stenosis and in most (75 per cent) aortic stenosis is also present. In fact, the degree of mitral stenosis is generally quite marked. It would therefore be impossible to distinguish the effects of one valve without considering those of the other valves.

Tricuspid endocarditis is still regarded as rare despite the fact that Dressler and Fischer<sup>6</sup> found that it was present in 24 per cent of all cases of rheumatic endocardial involvement. This closely corresponds to the figure obtained in this study (27 per cent). Several reports of individual or small groups of cases have been reported by various

\*It was the following experience (not included in this series) that crystallized in our minds some of the views concerning tricuspid stenosis and prompted this present study. A woman, aged 48, was seen in consultation with Dr. Phillip Marvel of Atlantic City in 1930. Some twelve or thirteen years before she had been examined by an out-standing consultant when she showed evidence of congestive failure, and the prognosis was estimated as a few weeks. She had such marked edema at that time that Southey tubes were used. Despite this bad prognosis, she carried on in moderate comfort for about fourteen years and even for two years after being seen by one of us. She showed obvious signs of mitral stenosis, auricular fibrillation, enlarged liver, ascites, and peripheral edema. Most of these signs had been present to a varying degree all these years. Because she had so much right-sided failure out of proportion to the degree of dyspnea for such a long time, a diagnosis of tricuspid stenosis was made. Post-mortem examination by her own physicians revealed stenosis of tricuspid, mitral, and aortic valves.

authors.<sup>7-15</sup> Although there was no instance of pure tricuspid stenosis in this series, such a case was reported by Clemens.<sup>16</sup>

The study of the age at death in different cases of tricuspid stenosis proved to be of some interest. Although the number of cases was small, the effects of the degree of tricuspid stenosis and of the additional valvular lesions were studied. Clinicians have long suspected that the presence of one valvular defect influences the course of events in the presence of another valvular defect. Likewise it has been thought that hypertension has a favorable effect on the progress of mitral stenosis.<sup>2</sup> It appeared from this study that with the same degree of mitral stenosis the presence of tricuspid stenosis and/or aortic stenosis tended to lengthen the duration of life. It was predicted that, when marked mitral stenosis is present, a moderate degree of tricuspid stenosis and a marked degree of aortic stenosis would result in the greatest longevity. Although only three cases in the entire series corresponded to these criteria, it is of interest that the average age at death of these three was 46 years, compared to the general average of all thirty-two cases of 34.3 years.

In the analysis of the clinical course of these cases, the duration of symptoms, and the age at death it appeared that the optimum pattern for a given degree of mitral stenosis was a slightly lesser degree of tricuspid stenosis, i.e., moderate tricuspid stenosis with marked mitral stenosis and slight tricuspid stenosis with moderate mitral stenosis. It was also evident that, from every angle investigated, those patients with moderate tricuspid stenosis did better than those with either slight or marked tricuspid stenosis. This latter observation might be looked upon as a corollary of the former statement inasmuch as most of the patients had marked mitral stenosis. An indication of the beneficial effect of aortic stenosis was observed when patients dying before the age of 30 years (twelve cases) were compared with those dying after the age of 40 years (nine cases). The former had distinctly less aortic stenosis than the latter.

One may speculate as to the significance of these curious relationships. In the development of the disabling complications of heart failure, peripheral edema and engorged liver (right-sided failure) are much less vital than pulmonary congestion (left-sided failure). There is comparatively little harm that results from even considerable edema of the legs. Even hepatic congestion may be present for many years and be compatible with an ambulatory existence. In the course of time this may result in depression in the liver function with hypoproteinemia or in cirrhosis of the liver with portal obstruction, but apart from abdominal pain and some other minor symptoms it does not play a dominant role in the causation of death. The main hazards with which most cardiac patients are faced are related to the lungs. Pulmonary

infection, infarction, and congestion with the resultant suffocation and lack of adequate oxygen exchange are the main causes of disability and mortality. With the development of mitral stenosis the concomitant presence of some degree of tricuspid stenosis serves to protect the pulmonary circuit by diminishing the return flow of blood to the lungs. With a normal tricuspid valve the vigorous contraction of an hypertrophied right ventricle keeps propelling blood into the pulmonary vessels too rapidly and in too great quantity to flow through a markedly narrowed mitral orifice. The result is stagnation in the lung, pulmonary congestion, and breathlessness. The diminished return to the right ventricle as a result of tricuspid stenosis partly offsets this imbalance. In a different manner aortic valvular involvement (or hypertension) may have a beneficial effect. They both would tend to enlarge and dilate the left ventricular cavity and stretch the mitral ring, thereby retarding the progressive constriction of the mitral stenosis. Furthermore, inasmuch as congestive failure is essentially the result of an imbalance between the two ventricles, hypertension and aortic valvular disease produce a burden on the left ventricle, and mitral stenosis, on the right ventricle; a better balance is thereby maintained. These physiologic and dynamic relationships help to explain the clinical observations relating to the effect one lesion has upon the other.

From a theoretical point of view, the left ventricle should be small in pure mitral stenosis and the right ventricle should be small in pure tricuspid stenosis because of the diminished work of the respective chambers. On the other hand aortic stenosis should cause left ventricular and mitral stenosis right ventricular hypertrophy. Because all cases in this study had combined lesions these relationships could be studied only by comparing those with different degrees of stenosis of various valves. In this way it appeared that tricuspid stenosis did tend to diminish the degree of right ventricular hypertrophy which was resulting from the accompanying mitral stenosis. This serves as further evidence of the protective action of tricuspid stenosis on mitral stenosis. Likewise it would be expected that all of these cases would show both left and right auricular enlargement, the former from the mitral stenosis and the latter from the tricuspid stenosis. This not only proved to be the case, but those with a higher degree of tricuspid stenosis had a greater degree of hypertrophy and dilatation of the right auricle. Accurate measurements of the capacity of the auricles were not made, but the fact that the right auricle can be enormous in tricuspid stenosis is illustrated by the case reported by Taussig<sup>14</sup> in which it was found to contain 2,150 c.c. while the capacity of the left auricle was only 95 to 100 c.c.

A very high incidence of pericardial adhesions was found among these cases (42 per cent). We interpret this as indicating that acute pericarditis is frequent in the early attacks of rheumatic infection in patients

who develop tricuspid stenosis. None of them, however, seemed to have the constricting type of pericarditis, although many of the extracardiac features of tricuspid stenosis closely resemble those seen in classical constrictive pericarditis. The fact that adhesions were less pronounced in those with marked than in those with lesser degrees of tricuspid stenosis would also tend to support the view that they had no relationship to the high degree of peripheral venous congestion.

The average weight of the liver was not as great (1,535 Gm.) as was expected, considering that the liver was practically always felt at a considerable distance below the right costal margin. Possibly because of the loss of body tissue and muscular tone that is so common in chronic cardiac disease, there is a certain degree of ptosis as well as enlargement of the liver. It is of interest that the weight of the liver was greater in cases of slight tricuspid stenosis than with more marked tricuspid stenosis. This may indicate that with prolonged stasis the amount of fibrous tissue may increase while the amount of blood decreases.

Ascites although a prominent feature in some cases was by no means always present. In a few cases in which determinations were made the blood proteins (mainly the albumin) were diminished. This probably was related to the damaged liver function, and, when present, must be an important factor in the production of edema and ascites. Increased venous pressure obviously is a further factor in the production of edema. This was always found elevated in tricuspid stenosis, and, as has been shown by Altshule and Budnitz,<sup>4</sup> remains elevated even when compensation is fairly well established and the patients are ambulatory. However, some cases of tricuspid stenosis may show no peripheral pitting. A third factor is the massaging effect of muscular activity that helps in the return flow of fluid from the legs. We believe that, when there is no hypoproteinemia and lack of dyspnea enables the patient to remain ambulatory (rather than inactive), the muscular activity of the legs helps to delay or prevent edema despite the high venous pressure.

As a result of the prolonged hepatic congestion many patients with tricuspid stenosis develop a peculiar icteric tint known to the older clinicians and discussed by Wearn.<sup>12</sup> It may be described as an olive discoloration of the skin which consists of a combination of slight icterus and slight cyanosis.

In our analysis of the relation between the time and number of attacks of rheumatic fever and the ultimate degree of valvular damage and age at death, certain significant observations were made. In the entire group there was a higher incidence of previous rheumatic fever or chorea (78 per cent) than is customarily obtained in routine hospital cases of rheumatic valvular disease. Despite this it appeared that the number of repeated rheumatic infections bore no relationship to the

severity of the cardiac damage, for cases with slight tricuspid stenosis had more frequent rheumatic bouts than those with more marked tricuspid stenosis. This would seem to indicate that the degree of endocardial damage is more closely related to the peculiar reactions of the host to the initial infection than to the frequency of repeated attacks. This somewhat presupposes that cardiac involvement began in all cases with the first infection which cannot be ascertained from our data. However, the average interval between the first rheumatic infection and death was about the same (20.6 years) for the various degrees of tricuspid stenosis. All this makes one suspect that the response of the individual host is an important factor in the development of rheumatic heart disease.

The clinical picture of tricuspid stenosis was well described by Shattuck, quoted by Futeher,<sup>9</sup> i.e., "whether a presystolic souffle can be heard or not, tricuspid stenosis can be pretty safely diagnosticated if the patient is a female with a rheumatic history, has mitral stenosis, perhaps also aortic disease and presents the evidence of prolonged or recurrent venous stasis of greater or lesser degree." In some cases abdominal pain due to the enlarged liver is a prominent feature. When the systolic pulsations are marked in the distended veins, one infers that the major defect is insufficiency of the tricuspid valve and, when they are absent, it is more likely that a high degree of stenosis is present. Venous distension is most significant if present in the upright position and while the patient is in a fair state of compensation. Pulsations of veins are often observed in the temporal vessels where they will not be confused with neighboring arterial pulsations. As was pointed out by Herrick,<sup>8</sup> patients may appear to be remarkably comfortable even though there are considerable edema, ascites, and cyanosis. Features suggestive of pericardial disease, simulating constrictive pericarditis, may be present, such as systolic retraction of the apex, Broadbent's sign, and failure of the heart to shift with change of bodily position. Considerable cardiac enlargement, the presence of valvular disease, and the marked precordial activity, however, practically rule out constrictive pericarditis.

The findings in the heart are mainly those seen in mitral stenosis. There will be marked cardiac enlargement, especially to the right. The pulmonary second sound will be increased in intensity but not, as a rule, to the same extent as in uncomplicated mitral stenosis. A regular rhythm will be found as frequently as auricular fibrillation, with an occasional case developing auricular flutter. It would seem that auricular fibrillation is not as common in tricuspid stenosis when marked congestive failure is present as is the case with mitral stenosis alone. The murmurs of mitral involvement will be heard at the apex (diastolic or presystolic and probably a systolic murmur). If these murmurs become louder or change their character toward the xiphoid region, one may suspect that

they have their origin in the tricuspid valve. Along the upper left sternal border and in the aortic area many cases will show a fairly loud systolic murmur and possibly a systolic thrill and even a blowing diastolic murmur. These latter signs indicate an accompanying aortic stenosis.

The findings in the chest will vary considerably. Some will have very little if any evidence of congestion and others will show few or many moist basal râles or the signs of hydrothorax. One is often struck with the paucity of pulmonary signs in the presence of marked peripheral and hepatic congestion. The liver is generally enlarged, palpable and pulsating, but absence of a palpable liver does not rule out tricuspid stenosis. On rare occasions the venous auricular "a" wave may be detected in tracings taken over the liver.<sup>6, 15, 17</sup> Hypertension is almost invariably absent and may be helpful in distinguishing patients with mitral stenosis and hypertension who do well for many years from those with mitral and tricuspid stenosis who similarly carry on for a surprisingly long time.

Laboratory findings are likely to show a high normal or slightly increased icteric index. Polycythemia may be present but is exceptional. One is more likely to find a high normal red cell count and hemoglobin level. Venous pressure will invariably be elevated. Excursions in the manometer will vary from 0.4 to 2.0 cm. of water with various phases of the cardiac cycle. The greater variations indicate a predominant element of tricuspid insufficiency rather than tricuspid stenosis.<sup>4</sup> The velocity of blood flow will be slightly slowed even in the presence of compensation and will be markedly slowed with congestive failure.<sup>4</sup> The serum proteins may be low and to some degree will determine the presence or absence of edema and ascites.

Roentgenologic examination may reveal calcification of the mitral or aortic valve, but the tricuspid valve has not as yet been identified in this fashion. Dilatation of the left auricle can easily be visualized, but the same is not true of the right auricle. Pulmonary congestion may be very slight considering the degree of heart failure. Electrocardiography may also be of some help. If right axis deviation is not present and some nonvalvular cause for left ventricular hypertrophy such as hypertension is absent, one should hesitate in diagnosing tricuspid stenosis. Practically all cases will show right axis deviation, and the few in which there is no axis deviation will have aortic stenosis. Ventricular complexes of low amplitude are common but generally are related to the presence of considerable edema. Such complexes tend to return to a normal voltage with the disappearance of edema. When the heart rhythm is regular, peculiar "P" waves indicating dilatation and hypertrophy of the auricles will almost invariably be noted.

A study of the comparative degree of stenosis of the three valves revealed certain interesting relationships. When the diagnosis of

tricuspid stenosis can be made and evidence of well-marked aortic stenosis can also be identified, one can be sure that the mitral valve will be markedly stenosed and the tricuspid at least moderately so. If the tricuspid valve is markedly stenosed, there will always be marked mitral stenosis.

The most significant aspect of this group of cases or the reason that more accurate diagnosis of tricuspid stenosis is of some importance is that one can give a much more hopeful prognosis after the onset of congestive failure than in any other type of chronic valvular disease. The average duration of life after the initial symptoms of congestion was 7.5 years. As has been reported before,<sup>13</sup> this is about twice as long as for other types of valvular disease.

#### SUMMARY AND CONCLUSIONS

1. In a study of 4,437 autopsies performed at the Peter Bent Brigham Hospital from 1913 to 1940 inclusive, there were 340 cases of chronic rheumatic valvular disease, of which thirty-two had tricuspid stenosis. These latter were equally divided into three groups, i.e., slight, moderate, and marked. There were an additional sixty cases of organic tricuspid involvement without a significant degree of stenosis.

2. The incidence of chronic rheumatic valvular disease in general and tricuspid stenosis in particular was 7.7 and 0.7 per cent, respectively, of all cases examined post-mortem. Tricuspid stenosis was found in 9.4 per cent of cases of chronic rheumatic valvular disease and in 14 per cent of cases of mitral stenosis. If those showing tricuspid involvement without stenosis are included, these figures are 27 per cent and 41 per cent, respectively.

3. Mitral stenosis (almost invariably marked) was found in 100 per cent and aortic stenosis in 75 per cent of the thirty-two cases of tricuspid stenosis. The degree of tricuspid stenosis was never greater than that of the mitral valve.

4. The average age at death was 34.3 years, which is considerably less than for other chronic valvular disease although the duration of heart failure was decidedly greater. Those with marked tricuspid stenosis died at a younger age than those with lesser degrees of stenosis.

5. Concomitant tricuspid stenosis and/or aortic stenosis was shown to have an effect on the progress of mitral stenosis. Aortic stenosis tended to shorten and tricuspid stenosis to lengthen the duration of failure although both added to longevity.

6. It was found that the clinical course largely depended on the correlation of stenosis of the three valves and that the optimum pattern for those having marked mitral stenosis was moderate tricuspid and marked aortic stenosis.

7. Pathologic studies showed that the average weight of the heart was 506 Gm. and that of the liver was 1,535 Gm. These figures seem smaller

than expected and their significance was discussed. Both auricles were almost always conspicuously dilated, especially the right. The degree of hypertrophy of the right ventricle was only moderate considering the marked mitral stenosis present. Chronic nonconstrictive pericarditis was found in half of the cases.

8. A past history of rheumatic infection was present in 78 per cent of the cases, but the frequency of rheumatic bouts had no relation to the degree of valvular stenosis or to the duration of life. It seemed that the peculiar reaction of the individual host was an important factor in determining the ultimate results.

9. The clinical picture seemed to depend upon the relative degree of stenosis of the aortic, mitral, and tricuspid valves. Practically all cases showed evidence of increased venous pressure, enlarged liver, marked cardiac enlargement (especially to the right), and a peculiar discoloration of the skin, consisting of a subicteric and slightly cyanotic tint. The extent of pulmonary congestion varied, and there was a notable absence of hypertension. The degree of edema and ascites was influenced by a lowering of the serum proteins. It is believed that tricuspid stenosis tends to delay the development of dyspnea and orthopnea that otherwise might occur in severe mitral stenosis by impeding the return flow of blood to the lungs.

10. Auricular fibrillation was present in about half of the cases despite the high degree of mitral stenosis, and those with regular rhythm died at an earlier age. Electrocardiograms almost always showed right axis deviation, and in those with regular rhythm the P waves were always of an abnormal form.

11. Mitral stenosis was diagnosed antemortem in all cases; aortic stenosis, in 50 per cent; and tricuspid in only five instances. The means for improving the accuracy of diagnosis of tricuspid stenosis and tri-ventricular stenosis have been discussed.

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# MECHANISMS INVOLVED IN ACUTE FATAL NONTRAUMATIC COLLAPSE ASSOCIATED WITH PHYSICAL EXERTION

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THE problem of acute, fatal, nontraumatic collapse during sport and work has recently been investigated by Jokl and Melzer (1940) and by Cluver and Jokl (1941). An analysis of sixty-six cases, in which clinical data as well as complete autopsy reports were available, revealed that collapse associated with exertion is almost invariably due to circulatory disease of long standing. In no case in which death occurred in connection with physical exertion was the subject found at autopsy to be free of serious disease.

## PATHOLOGIC FINDINGS

The following conditions, arranged in order of frequency, were found at autopsy:

1. Coronary artery disease.
2. Acute coronary occlusion.
3. Degenerative disease of heart muscle.
4. Ruptured aneurysm of aorta.
5. Chronic inflammatory disease of heart muscle.
6. Ruptured aneurysm of cerebral arteries, usually congenital.
7. Rupture of heart.
8. Rupture of congenitally diseased aorta.
9. Developmental abnormalities of the heart.
10. Developmental hypoplasia of entire arterial system.

Thus, of the three "master systems of the body" (Spillsbury, 1937), the circulatory, the respiratory, and the nervous, the circulatory is by far the most frequently involved in fatal nontraumatic collapse associated with work and sport.‡

## PATHOPHYSIOLOGIC CONSIDERATIONS

For the analysis of the functional mechanisms involved in the breakdown of the diseased circulatory system during exertion, the following physiologic reactions must be considered:

1. *The Biphasic Reaction of the Arterial Blood Pressure to Exercise.*—Physiologically arterial blood pressure rises during exercise and drops

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‡A tabulated account of the findings in each case is given in the S. Afr. J. M. Sc. 5: 4, 1940. A further report will appear in the AM. HEART J. (in press).

below the initial level during the rest period following exertion. We therefore speak of the "biphasic reaction to exercise." Whenever the autopsy revealed that death had been due to rupture of diseased blood vessels, it was ascertained that the first symptoms of the collapse which preceded death had set in *during* the muscular effort. As muscular exertion is accompanied by a rise of arterial systolic blood pressure, this physiologic reaction is therefore considered directly responsible for the rupturing of the affected blood vessels.

The phase of elevated blood pressure during exercise is followed by a depression during the rest period *after* the exertion, when the arterial pressure usually drops lower than the initial level. During this "negative phase," the significance of which for the coronary blood supply has recently been stressed by Blumgart, Schlesinger, and Davis (1940), there is distinct danger to subjects who suffer from coronary and myocardial disease.

Among our own cases was that of a football player who lost consciousness *after* a league match and died thirty minutes later. At autopsy his heart muscle showed general hypertrophy and advanced fibrosis. Another example is that of a 16-year-old girl who, having collapsed after dancing almost uninterruptedly for three hours, died a few minutes later. At autopsy, examination revealed congenital subaortic stenosis, marked hypertrophy of the left ventricle, and advanced myocardial degeneration.

2. *Expiratory Effort ("Valsalva" Phenomenon).*—We consider that expiratory effort with the closed glottis represents the greatest physiologic stress with which the heart has to cope.

The diffusion of oxygen through the lung is virtually suspended, and oxygen saturation of the capillary blood consequently decreases rapidly. This decrease has been shown by Matthes (1935) to be most marked during or immediately after exercise when the oxygen requirements of the tissues are raised. Moreover, the elevated intrathoracic pressure impedes the return of blood to the right auricle, leading to a sharp increase of systemic venous pressure (Baumann, 1935). The diminished output of the right ventricle as well as the greatly increased intrapulmonary pressure seriously interferes with the pulmonary circulation, leading to deficient filling of the left ventricle which through the fluoroscope can be seen to "beat empty" ("leerschlagen"). Thus, the filling of, and the pressure in, the ascending aorta decrease acutely, and the coronary blood flow consequently diminishes sharply. Visscher (1939) has drawn attention to what he calls "the pressure gradient mechanism" on which the coronary blood flow, like any other fluid in an hydraulic system, depends. "This pressure gradient," he says, "so far as the coronary system is concerned, is measured by the difference in pressure between aorta, and the coronary sinus and right

ventricle." As the intra-aortic pressure decreases during expiratory effort, the pressure gradient flattens and the coronary blood supply decreases sharply. Thus, myocardial respiration is greatly impaired. Although reflexes from the carotid sinus and aortic arch, in the face of a lowered aortic pressure, usually lead to a rise of *peripheral* arterial pressure due to arteriolar vasoconstriction (Bürger, 1935; Heymans, 1937), myocardial blood supply is likely to suffer greatly.

The profound pathophysiologic significance of this phase must be viewed in the light of the classic work of Shipley, Shipley, and Wearn (1935). These authors showed that a pathologically hypertrophied heart muscle possesses, per unit of myocardial tissue, a considerably smaller number of capillaries than a normal heart muscle. The area of myocardial tissue supplied by a single capillary, is enlarged in the pathologically hypertrophied heart. It exceeds greatly the equivalent area in the heart of the healthy, though untrained, subject. The richest capillary supply is found in the heart of the trained healthy athlete (Petren, Sjöstrand and Sylven, 1936). This is the reason why the heart of *trained healthy* subjects, whose respiratory tissue requirements are readily satisfied, will practically never be endangered, even in the course of strenuous athletic performances which demand extreme expiratory efforts, whereas, on the other hand, impeded myocardial blood supply implies a considerable risk in *all* situations, in which expiratory effort against the closed glottis occurs. Exercise represents one of these situations.

In subjects with coronary artery disease, and deficient capillary supply of a hypertrophic myocardium, this physiologic phase therefore often represents a catastrophic event from which the heart may never recover. Sudden death has frequently been encountered in middle aged and, occasionally, in young persons, in the course of physical activities, such as carrying heavy weights, gymnastic exercises, pushing a wheel-barrow, cycling up hill, or wrestling. In the majority of these cases autopsy revealed coronary and myocardial disease.

3. *The Gastrocoronary Reflex.*—Rise of intragastric pressure, especially, it is claimed, in the proximal portion of the stomach, elicits a reflex constriction of the coronary arterial system. The practical importance of the gastrocoronary reflex was first stressed by G. von Bergmann (1936) at whose clinic it had been investigated (Dietrich and Schwegk, 1933, 1934). Subsequently, the physiologic and clinical implications of this problem were carefully studied by N. C. Gilbert and collaborators (1939, 1940) and others. During physical exertion, when the oxygen requirements of the myocardium are considerably increased, the gastrocoronary reflex may result in serious anoxemia in the heart in which the tissue respiration is already impaired by disease. It has been shown by Jarisch and Liljeström (1927), that even the healthy circulation functions less economically if the stomach is dis-

tended, a result which represents the scientific basis for the empirical rule that after meals strenuous exercise is inadvisable. We therefore attach significance to the fact that in seven of our own cases the stomach was found distended with food. Two subjects were known to have taken part in strenuous games immediately after having consumed big meals. When they collapsed, they vomited very large quantities of undigested food, whereafter they experienced temporary symptomatic relief. Spilsbury (1937) reported the case of a young woman who collapsed while skipping after a meal and died shortly afterward. Autopsy revealed congenital absence of the left branch of the coronary artery. It may be assumed that in this instance the gastrocoronary reflex had caused a critical reduction of the oxygen supply to the myocardium.

#### PHYSICAL EFFICIENCY AND CIRCULATORY DISEASE

It is remarkable that cardiovascular disease, so serious that it may cause death at any moment, does not necessarily interfere with even an extraordinarily high standard of physical efficiency. Jokl and Parade (1933) described several cases of athletes with valvular defects. Jokl and Suzman (1940) have studied a marathon champion with aortic regurgitation and mitral stenosis. Suzman\* has recently observed a young wrestler who, in spite of the presence of mitral stenosis with enormous dilation of the heart and signs of congestive cardiac failure with cyanosis, continued, against advice, to take part successfully in wrestling bouts. Cluver and Jokl (1941) have communicated the case of "The Iron Man of South African Rugby," who died a few minutes after a test game in which he excelled in the same way as on innumerable previous occasions. Autopsy revealed a grossly underdeveloped abdominal aorta, an almost totally degenerated left, and a grossly hypertrophied right, kidney, a hypertrophied and degenerated heart muscle, an underdeveloped, partly obliterated, atheromatous coronary artery, and a large thymus gland, which, from the histologic appearance, could be assumed to have been functionally active. This collection of pathologic features must have been present for many years, and yet the "patient" had been one of the most outstanding rugby players in the world during the decade preceding his death. An identical twin brother of the deceased had died a short time before, also during physical exertion (swimming)!

We have included in this analysis only *nontraumatic* collapses. No reference is made to the large number of athletic fatalities of traumatic origin, most of which are due to injury to the central nervous system. As an example of this group, Jokl (1941) has recently analyzed a branch of sport (boxing) in which specific athletic traumata are frequently primarily responsible for fatal incidents. With regard to *nontraumatic*

\*Unpublished data.

fatal collapses during or after effort, the position is entirely different. A person who dies during exertion would, in most cases, otherwise have become the victim of some other physiologic activity. While normally no conceivable functional strain can cause fatal collapse (Suzman and Jokl, 1936), certain diseases, such as those enumerated in this paper, render heart and blood vessels so vulnerable that the physiologic effort associated with physical exertion may overtax their adaptive plasticity.

#### SUMMARY

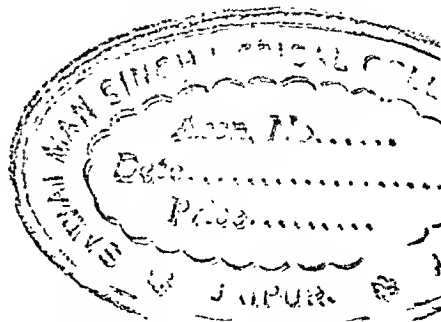
The results of an analysis of sixty-six cases of sudden death from physical exertion are discussed. The pathologic findings are given and interpreted.

A special attempt has been made to clarify the part played by physiologic reactions to exercises, in leading to the fatal breakdown. The following physiologic phenomena have been considered in detail: (1) The biphasic reaction of the arterial blood pressure to exercise, (2) expiratory effort (Valsalva phenomenon), and (3) the gastrocoronary reflex.

Attention has been drawn to the fact that even advanced circulatory disease is not necessarily accompanied by a decrease or a low state of physical efficiency.

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# THE COLD-PRESSOR TEST IN SUBJECTS WITH NORMAL BLOOD PRESSURE

## REPORT OF OBSERVATIONS ON 350 SUBJECTS, WITH SPECIAL REFERENCE TO THE FAMILY HISTORY

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ACCORDING to Hines,<sup>1</sup> "vascular hyperreactivity," as measured by the cold-pressor test, indicates "a prehypertensive phase of the syndrome which is designated as essential hypertension." He bases his conclusions on the observations that (1) hyperreaction to the cold-pressor test among people with normal blood pressure is similar to the reaction observed in essential hypertension; (2) patients who were formerly hypertensive show a hyperreactive response even though their blood pressure is normal; (3) the incidence of hyperreaction in children equals the combined incidence of hyperreaction and hypertension among adults; (4) subjects with normal blood pressure who show a hyperreaction generally come from families in which there is a high incidence of hypertensive cardiovascular disease; and (5) hypertension has developed in a few patients whose blood pressure was once normal, but who showed hyperreaction to the test.

We are presenting this series of observations on 350 people with normal blood pressure because our results with regard to the family history do not agree with those of Hines. As far as we know, there have been only two reports of cold-pressor studies, made with Hines' exact technique, which have included a larger number of subjects with normal blood pressure. In 1940, Hines<sup>1</sup> published the results of cold-pressor tests on 1,015 people with usually normal blood pressure, and Chesley and Chesley<sup>2</sup> have analyzed cold-pressor tests on 539 pregnant women.

### TECHNIQUE OF COLD-PRESSOR TESTS

The procedure as outlined by Hines was followed throughout. The subject reclined in a quiet room for a period of twenty to sixty minutes. Blood pressure measurements were made at intervals until a basal level was reached. The cuff of the sphygmomanometer was left on one arm, and, after the basal level was attained, the opposite hand was plunged into water at a temperature of 3 to 5° C. (37.4 to 41° F.). The hand was kept immersed to a level just above the wrist for sixty seconds. The blood pressure was measured at thirty and sixty seconds.

The difference between the basal level and the maximum reading is said to be the response. Using Hines' criteria, subjects whose response exceeded 20 mm., systolic, and 15 mm., diastolic, were called hyperreactors. Those whose response did not exceed these figures were designated as hyporeactors.

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## SUBJECTS OF TESTS, AND RESPONSE

The test was performed on 350 office workers with normal blood pressure. In so far as response to the cold-pressor test is concerned, they were selected at random. The blood pressure was arbitrarily said to be normal if it fell below 145 mm., systolic, and 95 mm., diastolic, after twenty minutes or more of rest in the reclining position. There were 260 men and ninety women. The average age was 37 years, and the range of age was 21 to 67. The results are summarized in Table I. The average response to the cold-pressor test was  $16.09 \pm 0.34^*$  mm., systolic, and  $15.67 \pm 0.30$  mm., diastolic. The range of response was -4 mm. to 56 mm., systolic, and 0 mm. to 45 mm., diastolic. There were only two subjects with a negative systolic response and none with a negative diastolic response. There were 104 hyperreactors (eighty males and twenty-four females), and the average response was  $27.68 \pm 0.45$  mm., systolic, and  $24.37 \pm 0.45$  mm., diastolic. Among the 246 hyporeactors (180 males and sixty-six females), the average response was  $11.35 \pm 0.21$  mm., systolic, and  $11.99 \pm 0.25$  mm., diastolic.

TABLE I  
SUMMARY OF RESULTS WITH THE COLD-PRESSOR TEST

| SUBJECTS      |        |       |         | MEAN RISE OF BLOOD PRESSURE IN MILLIMETERS OF MERCURY |                  |
|---------------|--------|-------|---------|---|------------------|
|               | NUMBER | MALES | FEMALES | SYSTOLIC  | DIASTOLIC        |
| Entire group  | 350    | 260   | 90      | $16.09 \pm 0.34$                                      | $15.67 \pm 0.30$ |
| Hyperreactors | 104    | 80    | 24      | $27.68 \pm 0.45$                                      | $24.37 \pm 0.45$ |
| Hyporeactors  | 246    | 180   | 66      | $11.35 \pm 0.21$                                      | $11.99 \pm 0.25$ |

TABLE II  
AGE AND HYPERREACTION TO THE COLD-PRESSOR TEST

| SUBJECTS         |        | HYPERREACTORS |            |
|------------------|--------|---------------|------------|
|                  | NUMBER | NUMBER        | PERCENTAGE |
| Entire group     | 350    | 104           | 29.7       |
| Ages 20-29       | 52     | 18            | 34.6       |
| Ages 30-39       | 205    | 54            | 26.3       |
| Ages 40-49       | 53     | 14            | 26.4       |
| Ages 50 and over | 40     | 18            | 45.0       |

Table II shows the effect of age on the response to the cold-pressor test. In the entire group, 104 (29.7 per cent) were hyperreactors. There were fifty-two subjects between the ages of 20 and 29, and, among these, eighteen (34.6 per cent) were hyperreactors. Among 205 persons between the ages of 30 and 39, there were fifty-four (26.3 per cent) who were hyperreactors. Between the ages of 40 and 49, there were fourteen (26.4 per cent) hyperreactors among fifty-three subjects. There were forty persons past the age of 50, and eighteen (45 per cent) showed hyperreaction to the cold-pressor test.

\*The figure after the sign is the probable error of the arithmetic mean.



THE FAMILY HISTORY

Table III shows that the response to the cold-pressor test was not related to the family history in the present series. One or more instances of hypertensive cardiovascular disease were found in the family histories of ninety-six (27.4 per cent) of the entire group when parents and siblings were counted. Thirty-one (29.8 per cent) hyperreactors and sixty-five (26.4 per cent) hyporeactors had such a family history. In an attempt to make an extreme comparison, the family histories of the subjects with a very high response to the cold-pressor test and those with a very low response were compared in the same way. There were thirty-four subjects with a systolic response of 25 mm. or more and a diastolic response of 25 mm. or more, and for convenience we have called them "high hyperreactors." There were forty-one with a systolic response of 8 mm. or less and a diastolic response of 8 mm. or less, and we have called them "low hyporeactors." Although these two groups are small, the results show the same trend that exists in the larger groups. In the family history of ten (29.4 per cent) of the high hyperreactors and eleven (26.8 per cent) of the low hyporeactors there were one or more cases of hypertensive cardiovascular disease. It can be seen that positive family histories among parents and siblings occurred with the same frequency in both hyperreactors and hyporeactors. The results were the same, regardless of the degree of hyperreaction or hyporeaction. These figures are greatly at variance with those of Hines,<sup>3</sup> who found positive family histories of hypertensive cardiovascular disease in 84 per cent of hyperreactors and 17 per cent of hyporeactors.

TABLE III  
COMPARISON OF FAMILY HISTORIES OF HYPERREACTORS AND HYPOREACTORS

| SUBJECTS      |        | ONE OR MORE CASES OF HYPERTENSIVE CARDIOVASCULAR DISEASE AMONG PARENTS AND SIBLINGS |            |
|---------------|--------|---|------------|
|               | NUMBER | NUMBER  | PERCENTAGE |
| Entire group  | 350    | 96  | 27.4       |
| Hyperreactors | 104    | 31  | 29.8       |
| Hyporeactors  | 246    | 65  | 26.4       |

All of the family histories were elicited by one of us, and exactly the same standards were applied in all cases, regardless of the blood pressure response. Our subjects, who were employed in the home office of a life insurance company, were probably more familiar with their family histories than people in general. The information was recorded as given from memory. The subjects were asked specifically as to the health, if living, or the cause of death, if dead, of each parent and each sibling, and then they were asked if their father, mother, brothers, or sisters had, or had had, high blood pressure, apoplexy, or heart trouble.

In many instances the subject knew the actual blood pressure level of the relative who had high blood pressure. Only cases of high blood pressure or of some illness which seemed likely to be the result of hypertension were counted. Sudden death caused by cardiac and cerebral accidents between the ages of 40 and 70 was considered as probably due to hypertension. If the subject could not definitely state that such an illness had occurred among his relatives, the family history was considered negative. There were a number of cases in both groups which were regarded as doubtful because the family histories showed cases of Bright's disease or heart trouble which could not be definitely classified. These cases were excluded from the positive group, but their inclusion would not have affected the result, for the proportion among hyperreactors and hyporeactors was the same.

TABLE IV  
FAMILY HISTORY AND RESPONSE TO THE COLD-PRESSOR TEST

| SUBJECTS  |        | MEAN RISE OF BLOOD PRESSURE<br>IN MILLIMETERS OF MERCURY |            |
|---|--------|--|------------|
|   | NUMBER | SYSTOLIC   | DIASTOLIC  |
| One or more cases of hypertensive cardiovascular disease among parents and siblings | 96     | 16.39±0.62   | 15.78±0.55 |
| No hypertensive cardiovascular disease among parents and siblings                   | 197    | 15.23±0.41   | 15.64±0.42 |

It is possible to show more clearly the irrelevancy of the family history in our series by comparing the blood pressure response among those who had a positive family history with that of those who had an absolutely negative family history. This analysis is shown in Table IV. Ninety-six of the 350 subjects had a positive family history of hypertensive cardiovascular disease among parents and siblings, and their response was  $16.39 \pm 0.62$  mm., systolic, and  $15.78 \pm 0.55$  mm., diastolic. Compare this with the response of  $15.23 \pm 0.41$  mm., systolic, and  $15.64 \pm 0.42$  mm., diastolic, among the 197 whose family history, with respect to parents and siblings, was negative. Statistically,\* there was no significant difference in the response between those with a positive family history and those with a negative family history. Our observations are quite in agreement with those of Chesley and Chesley,<sup>2</sup> who found a response of  $15.7 \pm 0.42$  mm., systolic, and  $18.3 \pm 0.42$  mm., diastolic, among 214 pregnant women with a family history of cardiovascular-renal disease or diabetes in parents and grandparents, as against  $14.6 \pm 0.28$  mm., systolic, and  $17.2 \pm 0.31$  mm., diastolic, in 320 subjects with a negative family history. If one agrees with most au-

\*The difference between the diastolic responses in the positive family history group and the negative family history group is so slight that it needs no comment. The difference between the systolic responses is 1.16 mm., which is 1.57 times the probable error in the difference of two means. Such a difference in one direction could occur fifteen times in 100 as a matter of chance, and, therefore, the difference is not "statistically significant."

thorities that the hereditary factor in essential hypertension is important, the belief that hyperreaction to the cold-pressor test indicates a prehypertensive state will have to be reconciled with these figures.

#### COMMENT

Since the subjects were selected at random, as far as response to the cold-pressor test is concerned, our results seem significant. The persons studied were employed in clerical capacities. They were asked to volunteer for the test, and this report covers the results on the first 350 volunteers with a normal blood pressure. There is no agreement among authorities as to what constitutes normal blood pressure. For this reason, we arbitrarily included all subjects whose basal blood pressure fell below 145 mm., systolic, and 95 mm., diastolic. Among the 350 subjects there were forty-six whose first blood pressure reading was more than 145 mm., systolic, and/or 95 mm., diastolic, although it fell below this during the observation. A trial analysis, omitting this group of forty-six, did not affect the incidence of positive family histories; therefore it was considered safe to include them. The subjects chosen for the test from among the group of volunteers were generally between the ages of 28 and 65. These age restrictions were the only form of selection we used, but here the effect of random sampling was not hampered because there was no foreknowledge of the blood pressure response.

Family histories of hypertensive cardiovascular disease can be taken in many different ways, and it is dangerous to make statistical comparisons of such histories when they are obtained by different observers. Some writers do not state just what relatives are included in their family history studies; others do not define what is meant by a positive family history. When the method of recording the family history is clearly described, as we have attempted to do, and when exactly the same criteria are applied throughout the study, it seems safe to make comparisons within the group observed. In our series the family histories were not known to us in advance, and the answers were recorded as given from memory. Our method was somewhat different from that of Hines, who obtained some of his family histories from records of the relatives themselves.

Fishberg<sup>4</sup> has said that "pending further evidence, it does not seem justified to regard a person as potentially hypertensive purely on the basis of a pronounced response to the cold-pressor test." Our results show nothing which would cause us to disagree with him. Dieckmann and Michel,<sup>5</sup> using a modification of Hines' technique on 101 subjects, and Briggs and Oerting,<sup>6</sup> who studied 233 subjects, have confirmed Hines' observations regarding family history and the response to the cold-pressor test. Our results in 350 cases and those of Chesley and Chesley<sup>2</sup> in a study of 539 subjects show no relationship between the response to the cold-pressor test and a family history of cardiovascular

disease. Together, these two groups include nearly 900 persons with normal blood pressure, and the results present a serious obstacle to the contention that hyperreaction to the cold-pressor test is an indication of a predisposition to essential hypertension. We agree with Hines that much more time must elapse before one can predict that a large number of hyperreactors will develop essential hypertension.

#### SUMMARY

Among 350 subjects with normal blood pressure, 29.7 per cent were found to be hyperreactors to the cold-pressor test. There was a family history of hypertensive cardiovascular disease in 27.4 per cent of the 350 cases. There was no relationship between the response to the cold-pressor test and the family history.

We are indebted to Mr. V. E. Henningsen, Assistant Actuary, for much valuable assistance in making the statistical analysis.

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## THE EFFECT OF PENTOBARBITAL ON THE CARDIAC CONDUCTION SYSTEM OF THE DIGITALIZED DOG'S HEART

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WHILE studying the effect of digitalis and magnesium on the cardiac conduction system of dogs, we were impressed by the changes which occurred when some of the animals were anesthetized with pentobarbital. That anesthesia may produce physiologic changes is not an unusual observation in experimental work, but, when studied with the electrocardiogram, it is rather striking. Halsey,<sup>1</sup> in his investigation of the effect of atropine and amyl nitrite on the electrocardiogram of the digitalized dog, abandoned the use of sodium luminal as an anesthetic because it prevented the development of the usual digitalis action. Since his interest was primarily in producing auriculoventricular block with a fair degree of regularity with digitalis, the effects of sodium luminal were not studied further. It is the purpose of this paper to report the effect of pentobarbital on the conduction system of digitalized dogs, and, conversely, the effect of digitalis on the anesthetized dog.

The effect of digitalis on the electrocardiogram of man was first studied by Nicolai and Simons,<sup>2</sup> in 1909. Since then a considerable amount of work has been done which has little bearing on this paper. Those who are interested in the bibliography should consult Larsen, Neukirch, and Nielsen.<sup>3</sup> The literature on the effect of digitalis on the electrocardiogram of laboratory animals is equally as voluminous. Earlier investigators<sup>4-9</sup> reported their experiments with digitalis bodies, especially strophanthin, and observed chiefly changes in the T wave. Slowing of the rate and prolongation of the conduction time were also recorded. Halsey,<sup>1</sup> Robinson and Wilson,<sup>10</sup> and Reid,<sup>11</sup> who used larger doses of digitalis, demonstrated ectopic impulses, auriculoventricular dissociation, and ventricular fibrillation. For a more complete description of the effect of digitalis on the heart one must consult the excellent monograph of Cushny.<sup>12</sup> Not as much, however, has been done on the effect of the barbiturates on the conduction system. Remé and his associates<sup>13</sup> took electrocardiograms on animals during pernocton and evipan anesthesia. They noted alterations in the electrocardiograms, but attributed the changes to anoxemia rather than to the anesthetic agents. Gruber and his co-workers<sup>14, 15</sup> were able to produce alternate ventricular rhythm in dogs, rabbits, cats, and monkeys

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with anesthetic doses of the thiobarbiturates. In dogs the P-R interval was shortened. Betlach,<sup>16</sup> on the other hand, observed no significant alteration in the electrocardiograms of dogs which were under the influence of amytal and pentothal. Similar results were obtained by Kohn and Lederer,<sup>17</sup> who studied the electrocardiograms of dogs, cats, rabbits, and monkeys which were receiving pentothal. Only a small percentage of the animals developed abnormal rhythms, and these consisted mainly of ectopic beats and disturbances in intraventricular conduction. The authors make mention of one experiment in which strophanthin was used. This drug produced marked changes in the electrocardiogram, but, after the injection of pentothal, the curve quickly returned to normal. Hafkesbring and MacCalmont<sup>18</sup> studied the effect of amytal, pentobarbital, and barbital on the conduction system of dogs and cats. The only cardiac effects of anesthetic doses of each of these agents, as shown by the electrocardiogram, were an increase in heart rate and a decrease in the sinus arrhythmia which is commonly seen in dogs and cats.

Clinically, Betlach<sup>19</sup> was unable to demonstrate changes in the electrocardiograms of hypertensive patients who had received sodium pentothal. Volpitto and Marangoni<sup>20</sup> were in agreement; they were unable to detect any changes in seventeen cases of pentothal, thioethamyl, and cvipal anesthesia.

#### METHODS

The unanesthetized dog was placed on the left side, and electrodes were attached to the right front and left rear legs (conventional Lead II). The dogs had been previously trained to lie quietly. Electrocardiograms were made with a string galvanometer type of instrument. All of the drugs were injected into the right saphenous vein.

Observations were made on seventeen dogs. Pentobarbital was selected arbitrarily because its action is short and it is frequently used in animal experimentation. The pentobarbital was administered in a 10 per cent alcoholic solution; each cubic centimeter contained 1 gr. (0.06 Gm.). At no time did the dosage exceed that usually required to produce surgical anesthesia, namely, 1 c.c. per 5 pounds of body weight. It was noted that less pentobarbital was needed to produce anesthesia in the digitalized than in the nondigitalized animal. The anesthetic was administered slowly (2 c.c. per minute), and discontinued when the corneal reflexes were abolished. The digitalis was given in the form of digalen; 2 c.c. were equivalent to 1 cat unit. It was administered rapidly in large doses, ranging from 1 to 1½ cat units per kilogram of body weight. This dosage was found adequate to consistently produce a marked digitalis effect.

#### RESULTS

*Experiment I.*—In this experiment fourteen studies were made. Control electrocardiograms were taken and digitalis was administered. The maximum digitalis effect was usually noted within thirty minutes,

at which time the pentobarbital was administered. In all but three experiments the observations were terminated within forty-five minutes after anesthesia. In the three exceptions the dogs were studied until consciousness returned. Electrocardiograms were taken at five-minute intervals.

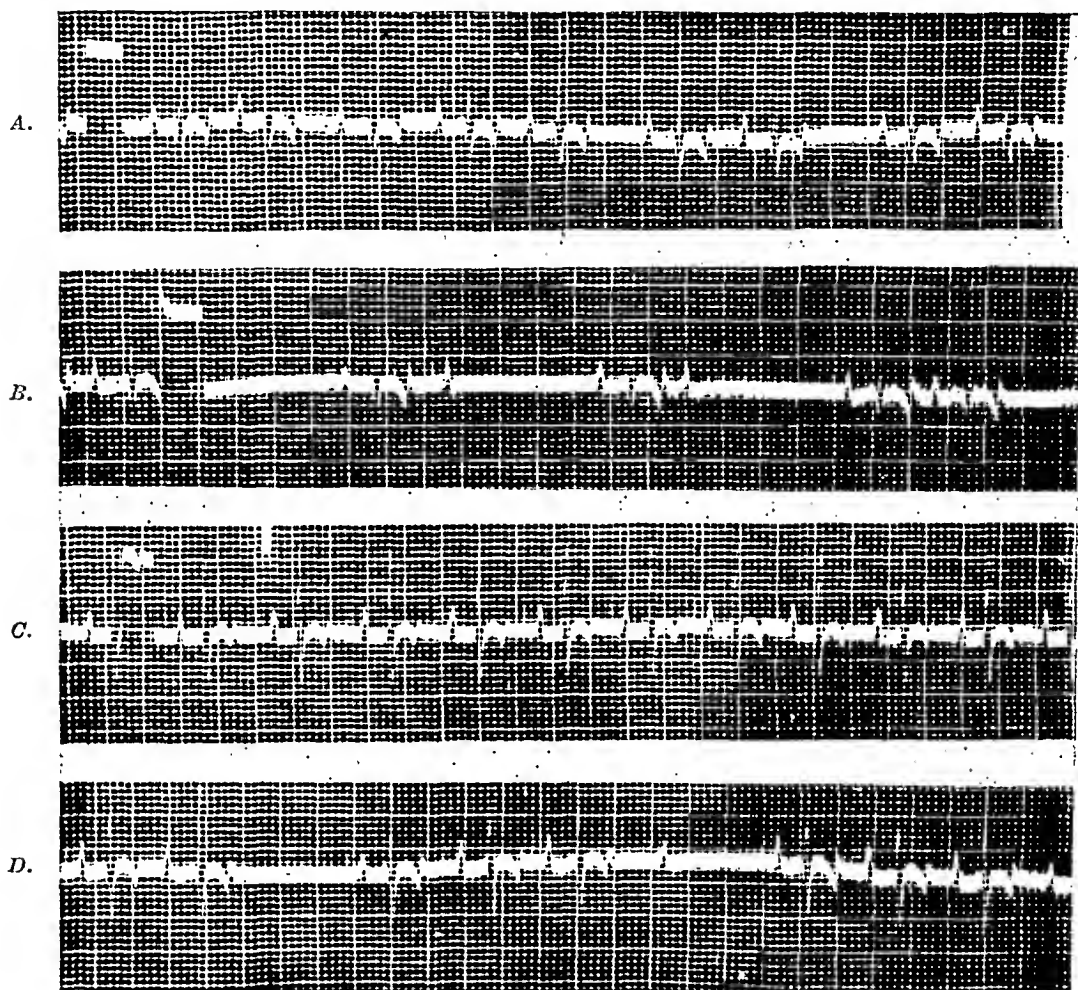


Fig. 1.—A, Normal. B, After the administration of digitalis ( $1\frac{1}{2}$  cat unit per kilogram). Complete A-V block. C, After the administration of pentobarbital. D, Twelve hours later. Residual digitalis effect still noted.

Ten (71.4 per cent) of these dogs responded to digitalis in the following manner (Fig. 1). The rate became slower by 20 to 40 beats, and the auriculoventricular conduction time increased by 0.02 to 0.04 second. In 60 per cent, partial or complete auriculoventricular block occurred. Nodal or auricular premature contractions were common. Blocked premature auricular systoles, as described by White and Sattler,<sup>21</sup> were noted. Ectopic impulses of ventricular origin were uncommon except in one experiment, in which alternating ectopic impulses of ventricular origin developed (Fig. 2). Sinus arrhythmia, which is so common in dogs, was seldom abolished, and T-wave changes were inconsistent.

When pentobarbital was given to the ten dogs mentioned above, two types of reactions occurred. In five animals the rate immediately became regular and more rapid and always exceeded the control rate. The P-R interval, which had been lengthened by digitalis, became shorter, and in some animals was less than the control measurement. In the remaining five dogs, pentobarbital produced an ectopic tachycardia of ventricular origin (Fig. 3). In one dog the ventricular tachycardia was produced only after additional pentobarbital was given; the smaller doses caused sinus tachycardia.

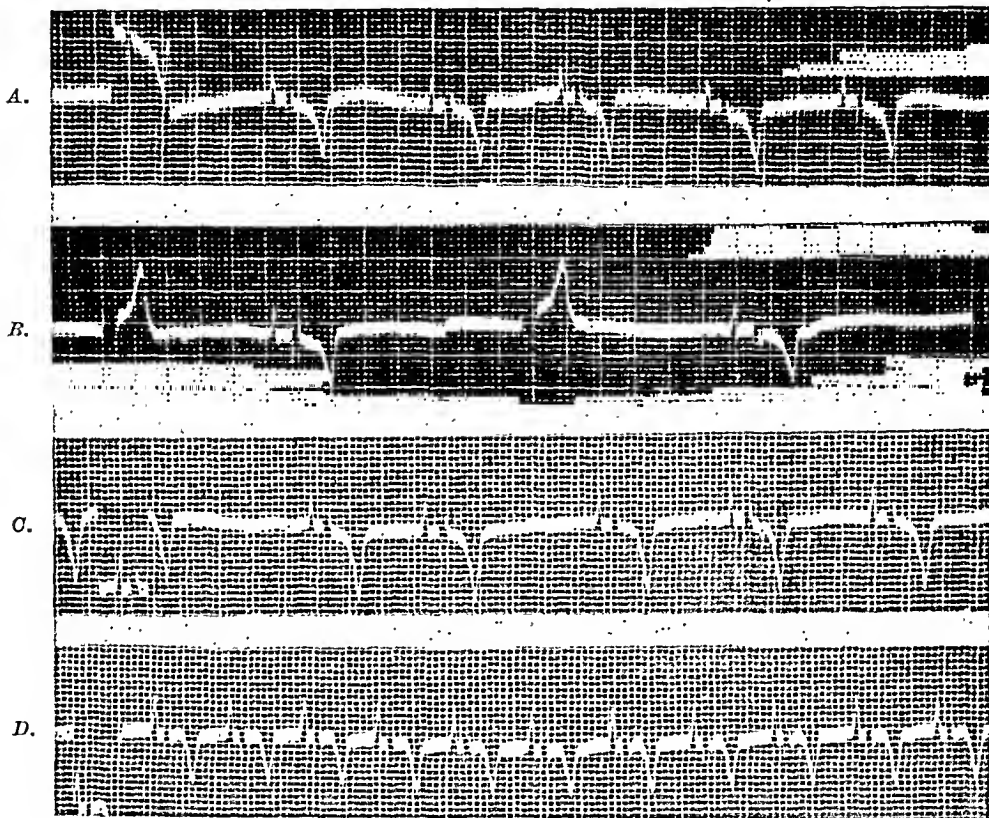


Fig. 2.—A, Normal. B, After the administration of digitalis. Note alternating ectopic impulses of ventricular origin. C, After the administration of pentobarbital. Sinus rhythm with increase in auriculoventricular conduction time. D, Twelve hours later.

In the dogs which were studied until they<sup>2</sup> became conscious, the electrocardiograms revealed sinus mechanism, with a residual digitalis effect.

When digitalis was administered to the four remaining dogs in this group, an ectopic tachycardia of ventricular origin developed (Fig. 4). The ventricular rate was usually 175 or more beats per minute, and two to five times as rapid as the auricular rate. The ventricular and auricular impulses were irregular, indicating not only independent rhythms, but also numerous ectopic foci in both auricles and ventricles. In this group pentobarbital had little effect except that of increasing the auricular rate.



*Experiment II.*—In this experiment three dogs were studied. They were first anesthetized with pentobarbital, and then given digitalis. After the administration of pentobarbital a definite increase in heart

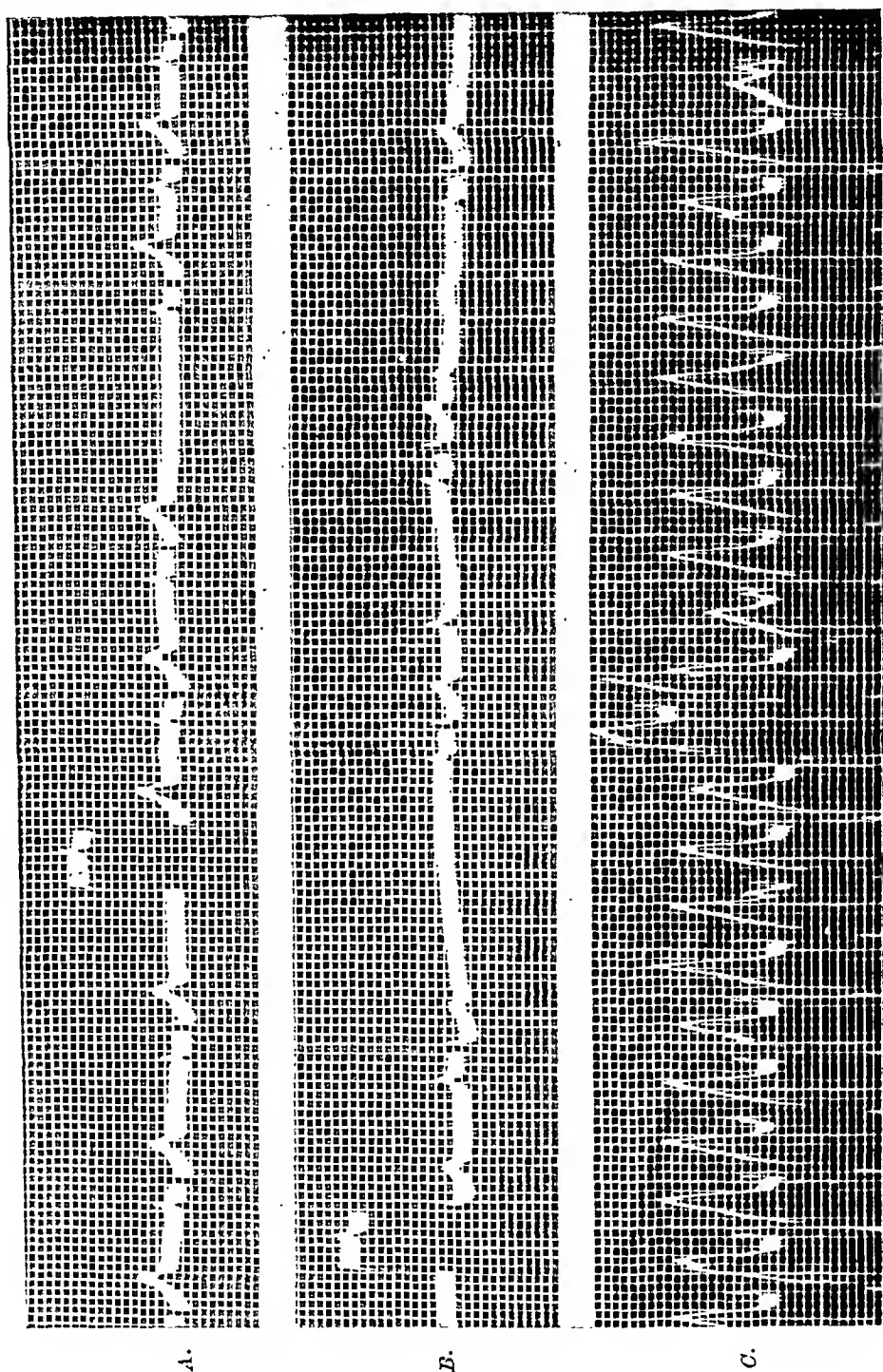


Fig. 3.—A, Normal. B, After the administration of digitalis. Usual digitalis effect noted. C, After the administration of pentobarbital. An ectopic tachycardia of ventricular origin was produced.

rate was noted. In two of the three dogs the auriculoventricular conduction time decreased 0.02 and 0.04 second, respectively. Pre-existing sinus arrhythmia was invariably abolished. These were the only changes. After the dogs were anesthetized, digitalis was administered in doses similar to those used in Experiment I, and its effect was found to be different from that on the unanesthetized dog. In the

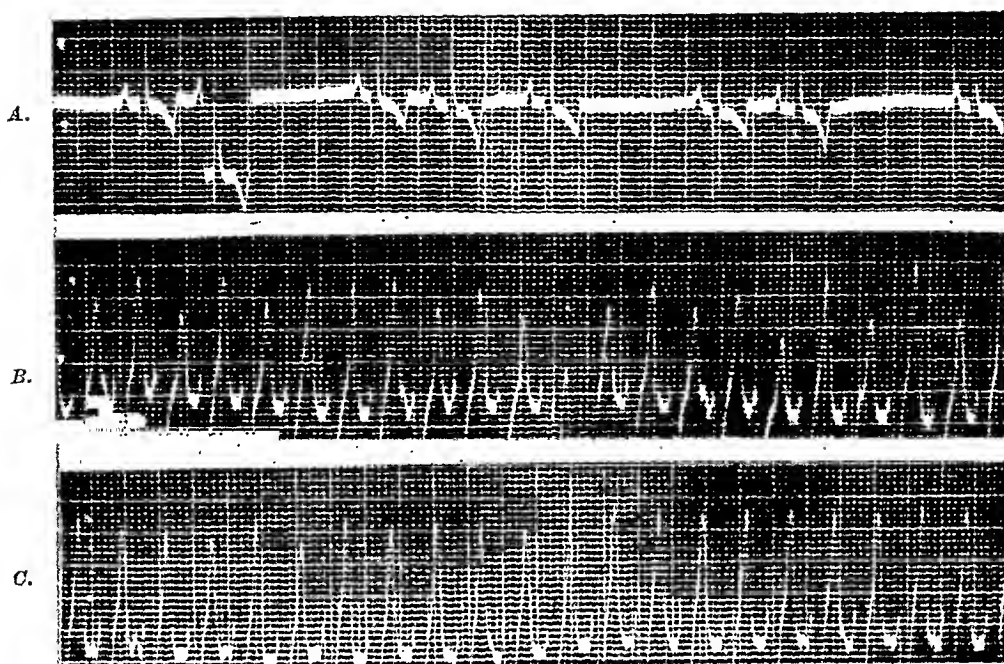


Fig. 4.—*A*, Normal. *B*, After the administration of digitalis. *C*, After the administration of pentobarbital. The ectopic tachycardia of ventricular origin remains unchanged.

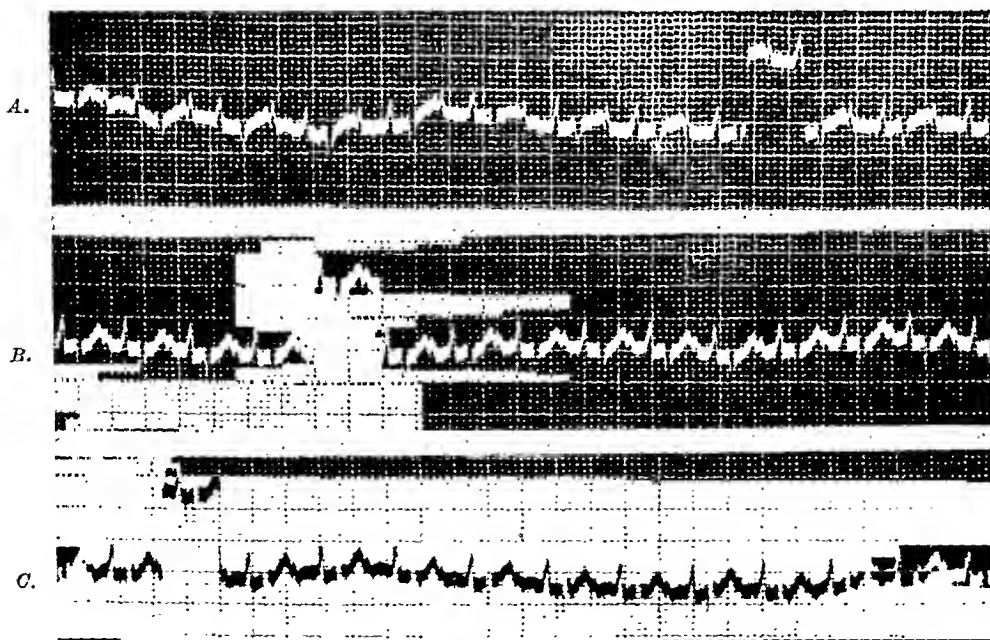


Fig. 5.—*A*, Normal. *B*, After the administration of pentobarbital. Note increase in rate and slight increase in auriculoventricular conduction time. *C*, After the administration of digitalis. Curve remains essentially unchanged.

first dog (Fig. 5) digitalis had no effect on the conduction system, as shown by the electrocardiogram. When this dog had been used in Experiment I, a typical digitalis effect occurred.

In the second dog, digitalis had produced, in Experiment I, alternating ectopic impulses of ventricular origin which were abolished by pentobarbital (Fig. 2), but in this experiment digitalis was capable only of slowing the rate and slightly prolonging the P-R interval (0.02 second). An electrocardiogram which was taken three hours later, after the dog regained consciousness, was not unlike the control except as to rate.

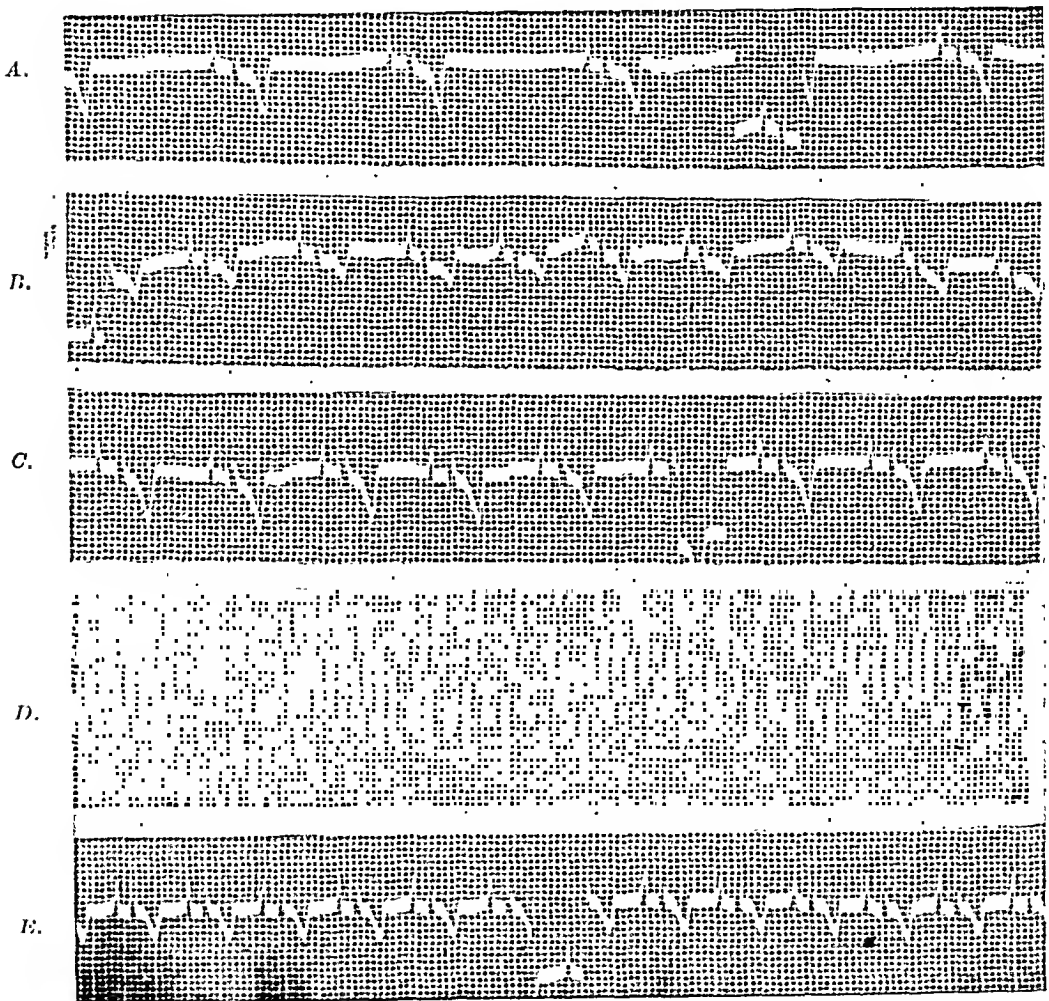


Fig. 6.—*A*, Normal. *B*, After the administration of pentobarbital. *C*, After the administration of digitalis. *D*, Ten minutes after the administration of digitalis. *E*, Four hours later. The dog was now awake.

After the administration of digitalis to the third dog, the rate became slower, and the auriculoventricular conduction time was prolonged. Within ten minutes, ectopic tachycardia of ventricular origin developed (Fig. 6). The latter did not occur when this animal was used in Experiment I. Electrocardiograms were taken four hours later, when the dog was again awake, and revealed sinus tachycardia with a normal P-R interval.

## COMMENT

The action of digitalis on the conduction system is well known and need not be discussed. The same cannot be said of the barbiturates. De Waele<sup>22</sup> reported vagus nerve depression from the effects of a mixture known as "Somnifene." In 1929, Lieb and Mulinos<sup>23</sup> called attention to the depressant and paralytic action of amytal on the cardiac vagus mechanism of the rabbit, cat, and dog. Garry<sup>24</sup> confirmed these observations and added the conclusion that amytal not only depresses, but, in some instances, completely paralyzes, the peripheral vagal ganglia. Since acetylcholine continued to be active during the period of amytal action, he concluded that the postganglionic fibers of the vagus were still responsive. He found that amytal was most effective on the vagus, whereas, in ordinary doses, phenobarbital was not effective at all. Shafer, Underwood, and Gaynor<sup>25</sup> studied the effect of sodium amytal on etherized, as well as decerebrated, dogs. In their decerebrated animals, amytal impaired the effect of vagus stimulation on the heart, and this depression could be surmounted by prolonged faradic stimulation of maximum strength. They observed some recovery of the vagus from the impairment, but in no case was the original, full, vagus inhibitory effect upon the heart regained, even after five hours of rest.

These observations were confirmed by Linegar, Dille, and Koppanyi.<sup>26</sup> In addition, they demonstrated that the effectiveness of different barbiturates varies considerably, in that amytal, pentobarbital, and per-noston are effective in moderate doses, whereas barbital was effective only when the doses were relatively enormous. Pilocarpine, when administered intravenously, was capable of diminishing, or even abolishing, this effect, which suggests that the action of the barbiturate on the vagus nerve was similar to that of nicotine and curare, rather than atropine. Phenobarbital had no demonstrable depressant effect. Swanson and Shonle<sup>27</sup> failed to demonstrate vagal depression with pentobarbital, but they used inadequate doses. Gruber and his associates<sup>28</sup> showed that barbiturates, when applied directly to the heart, produce paralysis not only of the ganglia, but also of the nerve endings.

It appears reasonable to assume that pentobarbital, since it has a depressant effect on the peripheral vagus ganglia, is capable of neutralizing the vagal action of digitalis. Atropine, which has a similar action, is capable of doing this. It is interesting to note the similarity between our results and those of Halsey,<sup>1</sup> who studied the effect of atropine on the conduction system of the digitalized dog. As long as the vagus is able to influence the various cardiac structures which are capable of initiating impulses, particularly the sinoauricular node, pentobarbital should be able to alter the effect of digitalis. This was found to be true in the early stages of digitalis intoxication, for pentobarbital abolished the usual bradycardia, auriculoventricular block, and premature con-

tractions. In the later stages of digitalis intoxication, when the ventricles became sufficiently irritable to produce an ectopic tachycardia, with complete dissociation between auricles and ventricles, pentobarbital was no longer capable of altering this rhythm except by increasing the auricular rate. Occasionally, pentobarbital appears to facilitate or bring about the occurrence of an ectopic tachycardia of ventricular origin in a heart which shows a moderate digitalis effect.

#### SUMMARY AND CONCLUSIONS

1. The effect of pentobarbital and digitalis on the conduction system of dogs was studied by means of the electrocardiogram.

2. Pentobarbital was found to alter the function of the conduction system in the digitalized dog.

3. Changes produced by digitalis, such as bradycardia, partial or complete auriculoventricular heart block, and ectopic impulses of ventricular origin, were abolished in five dogs by pentobarbital. In five other dogs pentobarbital produced ectopic tachycardia of ventricular origin.

4. When the ectopic tachycardia of ventricular origin was produced initially by digitalis, pentobarbital had no effect except to increase the auricular rate.

5. When digitalis is given to the dog which is anesthetized with pentobarbital, the usual digitalis response may not be elicited.

6. The action of pentobarbital on the conduction system is probably the result of its depressing effect on the vagus.

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## ERGOGRAPHIC STUDIES

### DESCRIPTION OF A NEW DEVICE, AND OBSERVATIONS ON NORMAL SUBJECTS AND ON PATIENTS WITH INTERMITTENT CLAUDICATION

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**I**NTERMITTENT claudication, which may be defined as symptomatic evidence of an inadequate blood supply to active muscle, is the earliest symptom in 51 per cent of all cases of thromboangiitis obliterans.<sup>1</sup> Often it may be the only clinical sign of occlusive arterial disease, and it may appear long before trophic lesions become manifest.

Although a great many methods are used to obtain qualitative and quantitative information about the blood flow through the skin,<sup>2, 3</sup> there are not many ways of estimating the supply of blood to the muscles in man without surgical intervention. Foster<sup>4</sup> and Silbert<sup>5</sup> described and used special thermocouples which, when inserted into the muscle belly, recorded changes in temperature; these changes were interpreted as indicating variations in the blood supply of the muscles. By this means, Silbert demonstrated the effect of certain drugs and various other procedures on the temperature of the muscles. This method, however, cannot be applied to active muscle, and is not ideal for general clinical work. Moreover, it remains to be demonstrated that this is a reliable method of ascertaining blood supply to muscles under any circumstances. Other authors (e.g., Pearl<sup>6</sup>) approached the problem by studying the changes in the skin temperature of the digits and using these changes to draw conclusions concerning the blood supply to the muscles of the extremity. Knowing that "it is no longer justifiable to conclude that an evident increase in the circulation of the skin is accompanied by a similar increase in the underlying muscles,"<sup>2, 3, 5</sup> it also appears unjustifiable to base conclusions about circulation in muscles on the presence or absence of skin temperature elevation after vasomotor paralysis, for these studies may indicate the status of the skin circulation only. A rise in skin temperature does not necessarily bear a definite relation to the amount of blood reaching the muscles. Elevation of the digital temperature as a result of peripheral nerve block seems to me to be neither sufficient reason for excluding the possibility

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of organic obstruction of the vessels supplying the regional muscles, nor sufficient justification for designating the cause of the claudication in such a case as "vasospastic."

In the literature of peripheral vascular disease, one usually finds the degree of intermittent claudication described in the following noncommittal manner: "the patient states that after walking three blocks he experiences pain." Naturally, the patient's own account of his symptoms is vitiated by various factors, such as differences in speed and gradient, and is thus of small value. Barker, Brown, and Roth<sup>7</sup> therefore estimated the degree of intermittent claudication by having the patient walk on the level at a standard speed.

Instruments designed to measure muscular work have been known as ergographs ever since Mosso<sup>8</sup> devised such an apparatus to study fatigue of the muscle of the middle finger and other related problems. Since fatigue of normal muscle is mainly a function of its blood supply, such methods may well be used for the study of the latter, and, in a number of instances, this has been done (Lewis, Pickering, and Rothschild,<sup>9</sup> Ratschow,<sup>10</sup> Simmons,<sup>11</sup> Hitzrot, et al.,<sup>12</sup> and Fisher, et al.<sup>13</sup>). I have constructed an ergograph which can be used to investigate the blood supply to the muscles of the lower extremity.

#### APPARATUS\*

Ratschow's and Simmons' apparatus consists mainly of an inclined foot splint, serving as a support for the leg, on which an upright foot piece is fixed by means of a pair of hinges. The axis around which the plantar or dorsal flexion of the foot normally takes place passes through the malleoli, and not through the end of the calcaneus, to which the hinge in such an apparatus corresponds. Furthermore, with such an arrangement the subject cannot control his movements, and therefore the weight is lifted to various heights by different subjects, which gives uncomparable results. No tracing can be obtained. The ergograph which has been employed in our studies differs in many respects from any other type in use for the lower extremities. It consists mainly of four parts (Fig. 1*A* and *B*), namely, the ground board (*G.B.*), upon which are fixed the support for the leg (*L.S.*), the foot piece (*F.P.*), and the upright board (*U.B.*). The shape of the leg support, which is fitted at a height of 10 cm., inclines somewhat toward the foot piece. Special care was taken in constructing the foot piece (*F.P.*), upon which the adjustable foot piece proper (*F.P.p.*) is fixed with two bolts which slide in slits (*S*) to allow adjustment of *F.P.p.* The foot piece proper is fitted with a heel and toe cap and two leather belts to fix the foot of the subject. The foot board (*F.P.*) is suspended in such a way that it can easily be moved around an imaginary axis passing through the joints *A* and *B* and through the malleoli of the foot when it is fixed on the foot board. It is this suspension of the foot piece which enables the foot to rest comfortably and firmly, with its whole surface upon its support, during the movements. A screwing bolt (*Bt*) permits adjustment of the amount of initial plantar flexion, and a string with a screw fixed on both *F.P.* and *U.B.* enables one to adjust the initial amount of dorsal flexion. The upright board, *U.B.*, is fitted with a metal

\*I am indebted to Mr. G. McManus, laboratory assistant in this department, for his valuable help and suggestions during the construction of the apparatus.



arm, *M.A.*, bearing pulley 1, the scale, and several pulleys (2, 3, 4, 6, 7, and 8) which are partly fitted in openings of the board to guide the various strings. The upright board is kept in place by a triangular piece (*T.P.*) which has a square opening to take the screw wheel (*S.W.*) to bolt *Bt.* It also holds pulley 5. Two strings (*X* and *Y*, Fig. 1) are attached at the end of the foot board, both of which, after running over a number of pulleys, lead to the weight (*W*) gliding up and down in a cage (*C*): Depending upon which group of muscles is to be tested,

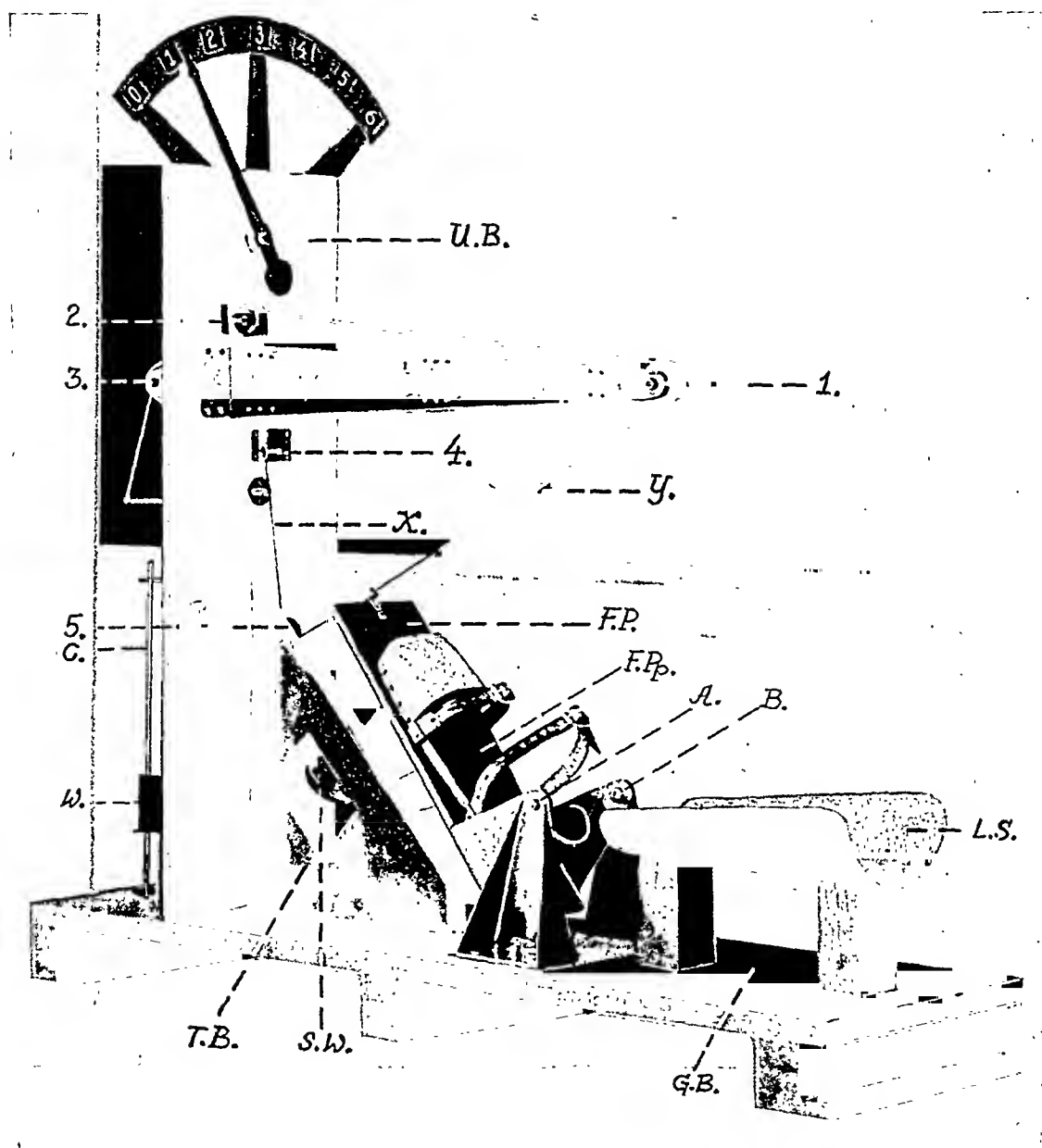


Fig. 1A.—Ergograph for ascertaining the claudication index in the lower extremity.

either dorsal or plantar flexion of the foot will be required. For dorsal flexion (anterior tibial group), string *X*, leading from *F.P.* over pulleys 5, 4, and 3 to the weight, will be used. For plantar flexion, string *Y*, leading from *F.P.* over pulleys 1, 2, and 3, will carry the weight. The indicator on top of *U.B.* is worked by string *Z*, leading from the side of the foot board over pulley 7 to pulley 8. In the same way, string *Q* is fixed at the side of *F.P.*, runs over pulleys 6, 9, and 10, and works

a lever on the paper of a kymograph. With  $Q$  and  $R$  fixed at different heights on the side of  $F.P.$ , the excursion of both the indicator and the recording lever can be adjusted within wide limits.

The subject rests upon a bed in a half-reclining position. The upper part of the leg is bent in an angle of  $120^\circ$  against the body, and the lower and upper parts of the leg form an inner angle of approximately  $135^\circ$ . The leg to be investigated is fixed in the ergograph, and, during the test, the subject moves his foot according to the beat of a metronome.

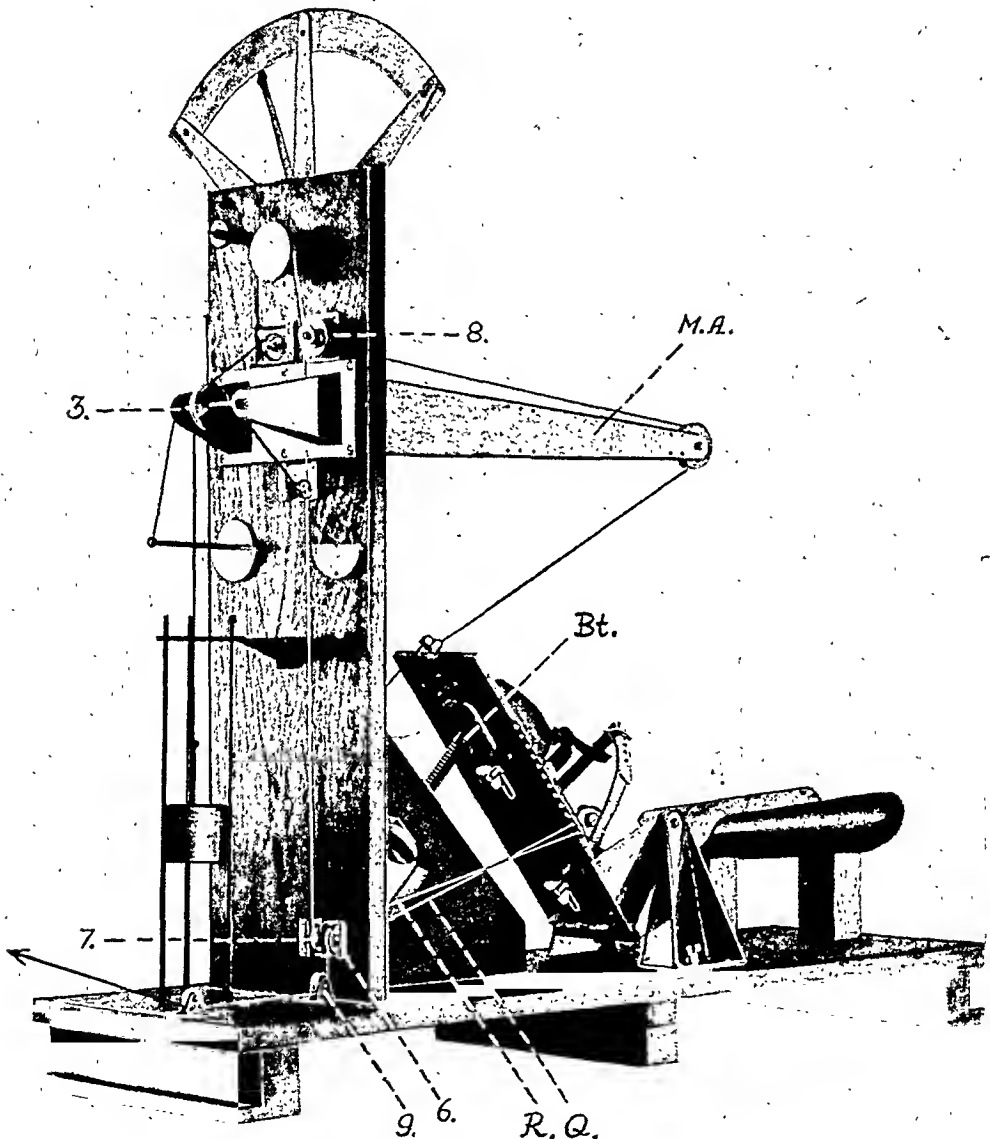


Fig. 1B.—Ergograph for ascertaining the claudication index in the lower extremity.

#### RESULTS

When a person with either a normal or an impaired arterial circulation performs dorsal or plantar flexion of his foot, thereby elevating a

given weight, his muscles soon tire, but this does not prevent his flexing the foot to the original extent. If he continues the work, pain develops, and, with further exercise, becomes so severe that full flexion is impossible. Eventually, he is compelled to give up the exercise completely (Fig. 2A and B). The pain vanishes within a few seconds after stopping the exercise, and a dull aching and sense of heaviness persist for some time. Paresthesia may be experienced. Patients who have intermittent claudication in one leg, and exercise the "unaffected" leg first, describe the pain as being exactly of the same character as that which they experience in the affected leg when they walk.

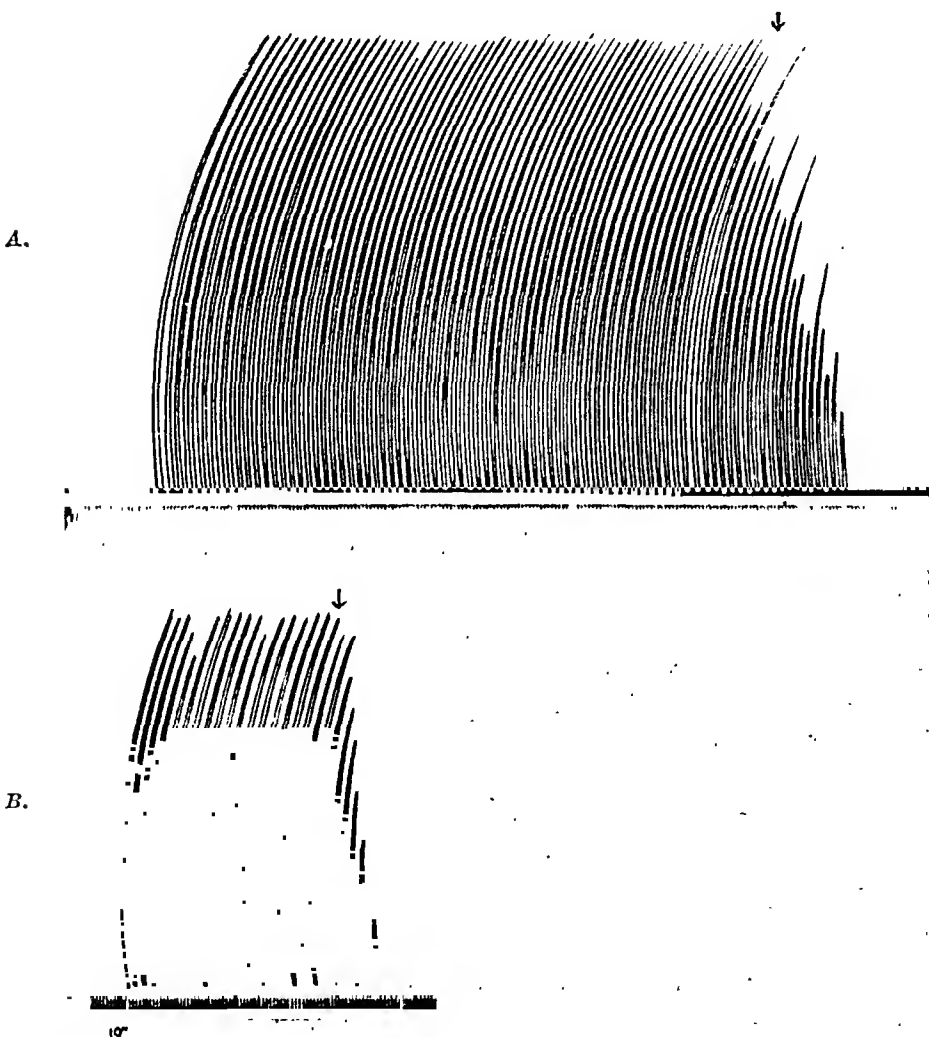


Fig. 2.—Ergograms of a normal subject (A) and of a patient with advanced thromboangiitis obliterans (B). Fifteen hundred grams lifted 25 cm. by dorsal flexion.

The results of all ergographic studies, if voluntary contractions are recorded, depend upon the volition of the subject.\* We tried to overcome this difficulty by arranging the indicator, with its scale, on top of

\*The results of investigations in which the muscles were electrically stimulated in order to exclude the volition of the subject will be dealt with in another publication.

the apparatus, so that the subject could control his movements. In this way it was also possible to obtain the same elevation of the weight in all cases by asking the subject to move only between two given marks on the scale.

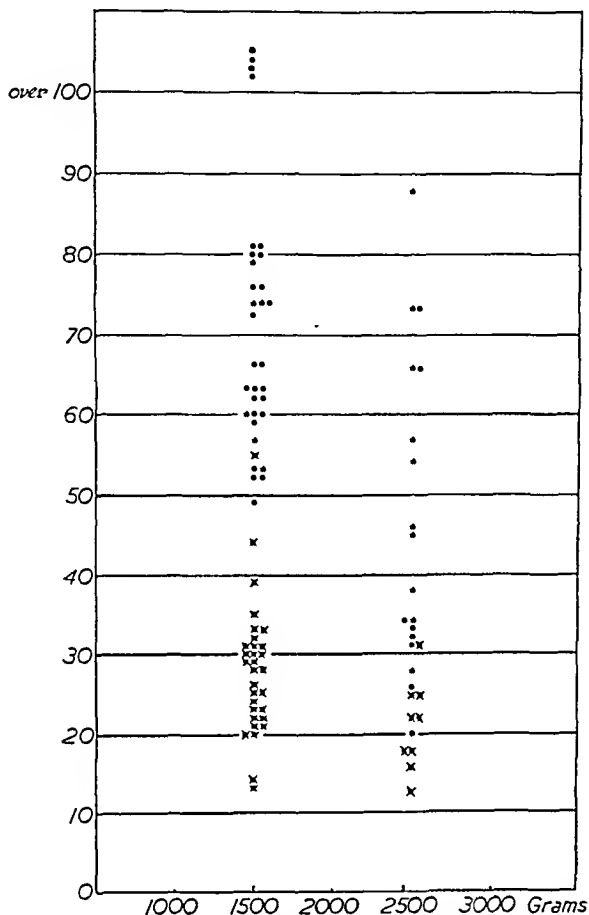


Fig. 3.—Claudication indices of normal legs (dots) and abnormal legs (crossed dots) after lifting 1,500 Gm. and 2,500 Gm., respectively, to a height of 25 cm. by dorsal flexion.

All previous authors have used either the total amount of work of which the muscles were capable, or the time of onset of pain, for evaluation of the results; this introduces a subjective factor in ascertaining the end point. Investigation has taught us that the time of onset of the pain depends much upon the subject, and what he considers worth noticing. It was found to be a reliable criterion only when various results on one subject were compared. Comparable results on different subjects were obtained by counting the number of complete contractions, rather than by measuring the amount of work performed or observing the time of onset of pain. Naturally, the number of full contractions will be dependent upon the amount of work performed, and this, in turn, will depend on the height to which the weight is lifted. If the number of contractions are plotted against the various heights to which the weight has been lifted, a paraboliform graph is

obtained. In Fig. 3 the values obtained on twenty-five normal and forty abnormal subjects have been plotted against two different heights; all other conditions were identical. Elevating 1,500 Gm. results in a distinct distribution of the indices of both the normal and the abnormal subjects. This gives way to considerable overlapping if the weight is increased to 2,500 Gm. Weights of less than 1,500 Gm. did not regularly exhaust the muscles. From this it is apparent that, in our experiments, using a weight of 1,500 Gm. gave significant results. For dorsal flexion, the optimum weight was 1,500 Gm. (lifted 25 cm.), and, for plantar flexion, 7,000 Gm. (lifted 25 cm.). One and one-half seconds for contraction, alternating with one and one-half seconds for relaxation, was the rhythm which was found to be most reliable. The number of full contractions which was obtained under these standard conditions was used in all subsequent experiments as a criterion and is referred to as the *claudication index*.

#### DISCUSSION

Starting from the fact that the efficiency of muscular work is to a large extent a function of the blood supply, the ergographic methods which are usually employed for physiologic investigation of muscular fatigue may be successfully applied in the study of the muscular ischemia which causes intermittent claudication. The method may be used to differentiate other forms of pain in the legs (caused by neuritis, flat foot, arthritis, and varicose veins) from intermittent claudication, although the experienced clinician seldom needs such help. Valuable objective information concerning the effect and progress of therapy may be obtained, especially in cases in which no trophic lesions are present. The advantage of having a record for further reference is substantial.

#### THE CLAUDICATION INDEX OF THE NORMAL SUBJECT UNDER ORDINARY LABORATORY CONDITIONS

As stated previously, it has been found that the most reliable criterion of blood supply to muscle is obtained by counting the number of full contractions, rather than by estimating the total amount of work of which the muscles are capable. This index, which is obviously proportional to, if not identical with, the walking capacity of the patient, is called the "claudication index."

This claudication index depends not only on the amount of work being performed, but also on certain intrinsic factors, of which the development of the muscles and the age and general psychic state of the subject are important. Therefore, there is a considerable range in the values of the claudication index among normal subjects, even if the material which is used appears to be homogeneous. From Fig. 4, which gives the distribution in the group of normal persons, it is evident that, in thirty-six

of thirty-seven subjects (97 per cent), the claudication index was above 50, and that, in thirty-three subjects (84 per cent), it fell between 50 and 90. In only one clinically normal person (52 years of age) were the indices for one leg found to be constantly in the 40 to 50 range. Values considerably higher than 90 were observed in three instances. Thus it appears that any index below 40 must be considered definitely abnormal. The indices for the two legs are usually within the same range, regardless of whether the subject is right- or left-handed. However, when marked differences were observed, the higher value was regularly found in the right leg of right-handed persons, and vice versa. The results were very constant, even when the observations were made at intervals of as much as a year or more. No definite relation between the indices and vasomotor tone could be detected, but this will be the subject of further study.

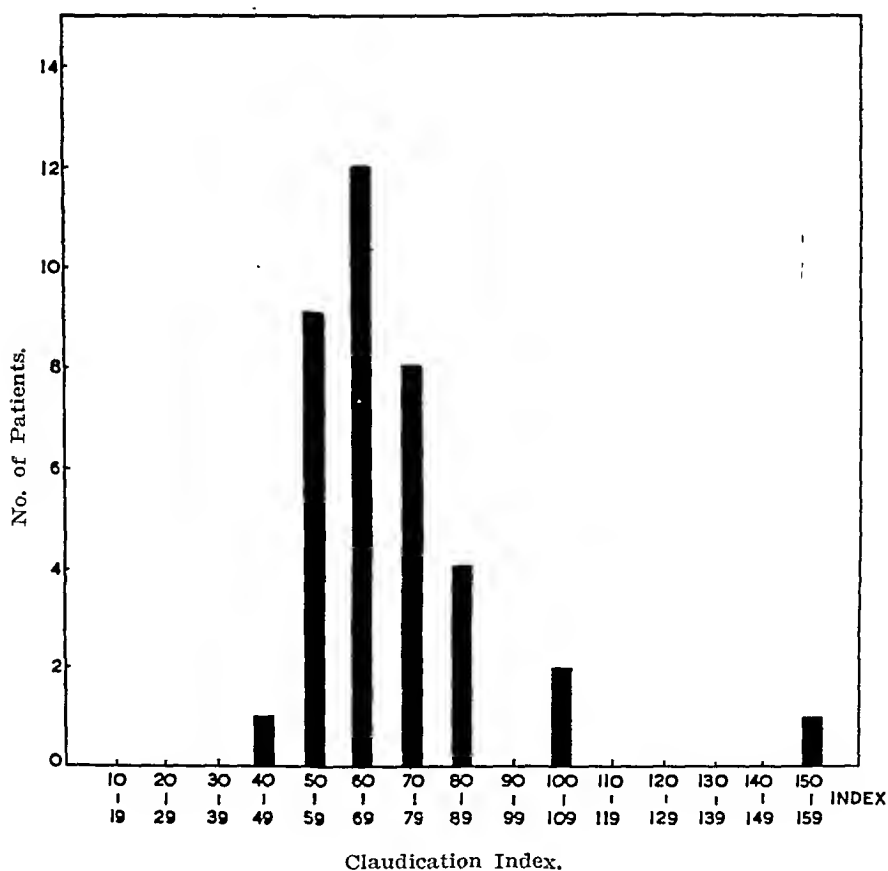


Fig. 4.—Claudication index in normal subjects.

#### THE CLAUDICATION INDEX IN CASES OF CHRONIC, OCCLUSIVE, ARTERIAL DISEASE

Thirty-eight patients with intermittent claudication were studied; twenty-six had thromboangiitis obliterans, and twelve had arterio-sclerosis obliterans. Not only is there a marked diminution of the

claudication index in occlusive arterial disease, depending, naturally, upon the degree of the pathologic changes, but there is also a very steep decline after the last full contraction. It has been found that indices taken on different occasions are extraordinarily constant. The indices

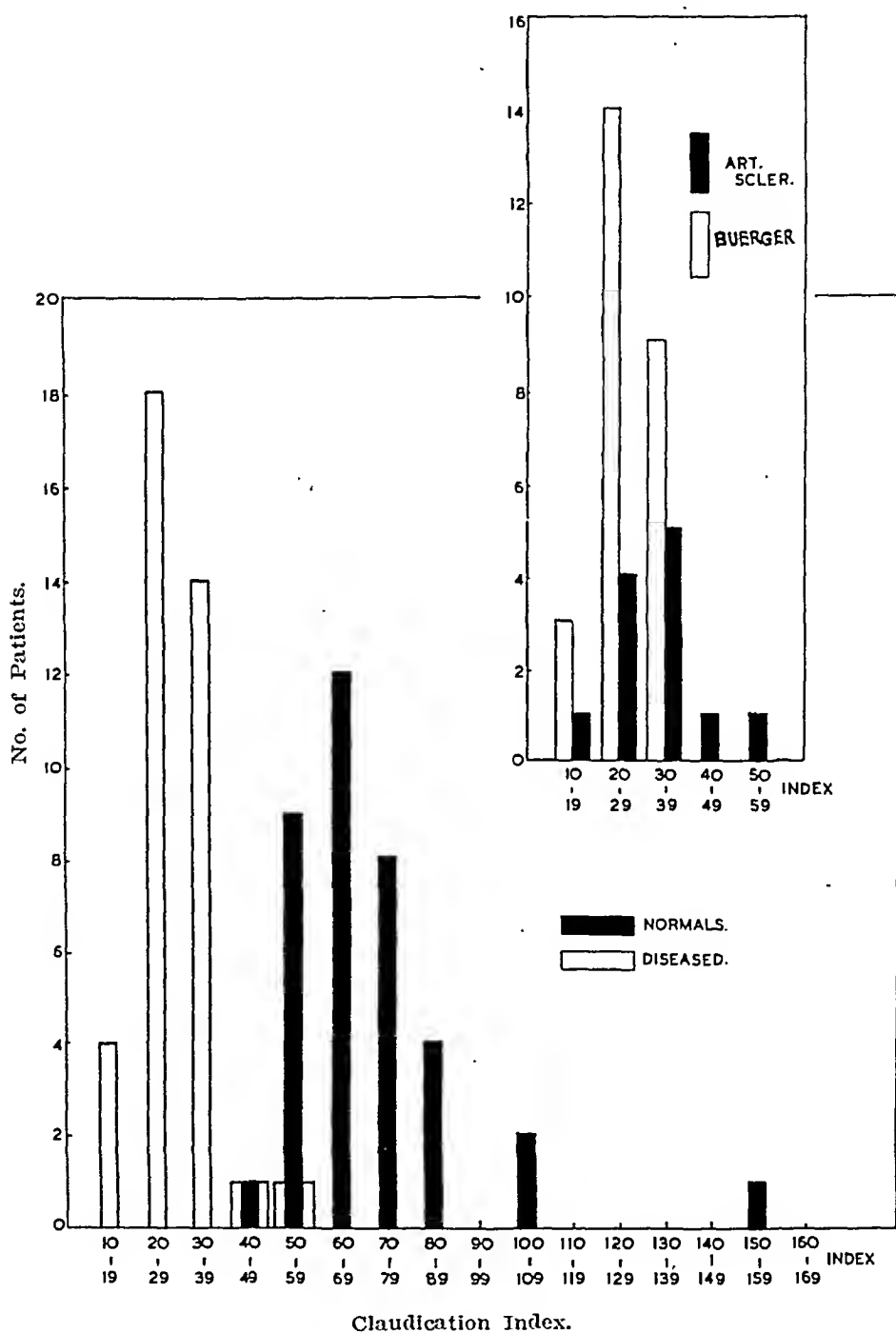


Fig. 5.—Claudication indices in cases of intermittent claudication.

in thirty-six of thirty-eight (95 per cent) of our cases were below 40, with a peak in the 20 to 30 range (Fig. 5). In two cases of arterio-sclerosis obliterans, associated with a mild degree of intermittent claudication, in which there was a good collateral circulation, as judged

by the skin temperature and plethysmographic measurements, the claudication index was above 40. In the case in which the indices on the two sides were 56 and 58, respectively, the complaint was more of fatigue,

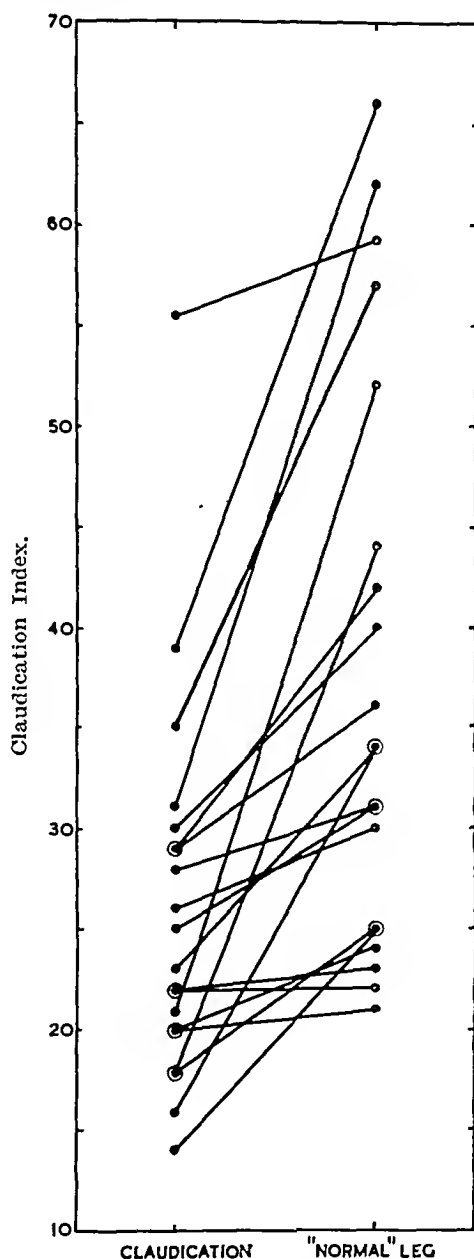


Fig. 6.—Relation between the claudication indices of the two legs of patients with a history of intermittent claudication in only one leg.

after a walk of about one mile, than of real pain. It has been found that the index is usually in close agreement with the severity of the clinical manifestations. The shorter the walking distance until claudication appears, the lower the index. On the other hand, it could be proved that, in cases in which the claudication was supposed to be severe, but the claudication index was high, the history did not correctly portray



the true state of affairs. There is no definite difference in the range of the claudication indices in thromboangiitis obliterans and arteriosclerosis obliterans (Fig. 5).

Although the patients usually complained of claudication in one leg only, the other leg, in many cases, especially when the disease was severe, also showed a reduced index, indicating bilateral involvement which was not apparent clinically (Fig. 6). Only in a small group of cases was the index of the unaffected leg still within the normal range (above 50); in most cases it was distinctly reduced. It may therefore safely be concluded that the circulation in the "unaffected" leg is usually already considerably impaired, an observation which in most, if not all, cases could be confirmed by other methods. It is only because exhaustion of the more affected leg takes place first, and forces the patient to stop, that the impairment of the circulation in the "unaffected" leg does not become obvious during walking. Often there is a difference of only 5 to 6 in the claudication indices of the two legs, but this is sufficient to make the claudication unilateral. As shown in Fig. 5, in most of the cases of moderate claudication there is a bigger difference between the indices of the two legs if one leg still has normal, or almost normal, values. As the occlusive process progresses, the indices in the two legs are found to be more and more within the same range, until the originally less affected or unaffected leg may appear worse than the one which was involved first. As the disease advances, the claudication index decreases until, in the patients with rest pain, it becomes almost zero. This decrease can be followed up. In one case of thromboangiitis obliterans a year elapsed between the tests; the index decreased during that time to almost half its original value, indicating further impairment in the blood supply to the regional muscles. This agreed well with the history, which was to the effect that the condition had become much worse during that year.

#### THE CLAUDICATION INDEX AFTER EXPERIMENTAL ARTERIAL OCCLUSION

That the onset of claudication and the height of the claudication index are dependent upon the blood supply of the muscles can be readily demonstrated by experiments in which the arterial blood supply to the exercised limb has been stopped suddenly (Fig. 7). Thus the conditions which obtain in disease can be simulated in the normal subject. The claudication indices of the normal subject after arterial occlusion are not only greatly reduced, but agree remarkably well with those in cases of severe intermittent claudication. In cases of advanced claudication, in which there are a low index for the leg concerned and a relatively high one for the unaffected leg, experimental arterial occlusion will reduce the index for the unaffected leg to a value within the same range as that recorded for the diseased leg. The low indices in cases of severe

claudication might therefore be regarded as indicative of almost complete arterial occlusion in the region of the muscle which becomes painful. However, the amount of blood trapped in the leg by the cuff which is used to produce experimental arterial occlusion may supply a considerable amount of oxygen, and therefore the assumption in the foregoing sentence might well be false. Normally there is a big difference between the claudication indices before and after experimental arterial occlusion, but this is not true of the abnormal leg. In cases of advanced occlusive arterial disease the difference is very small. The difference between the indices before and during experimental occlusion may therefore be used as a rough measure of the circulatory reserve in the region of the exercised muscle. The bigger the difference, the less obstruction and the more circulatory reserve. With an advanced degree of obstruction there is less circulatory reserve, as indicated by a small difference between the two values. It may be mentioned that, when the claudication index of the nonaffected leg was ascertained during experimental occlusion, the patients regularly volunteered that the pain in that leg during the procedure was absolutely identical with that experienced in the affected leg after walking.



Fig. 7.—Effect of experimental arterial occlusion on the claudication index of the normal subject. A, ergogram before, and B, ergogram after, inflating a cuff above the knee to 200 mm. Hg (blood pressure, 120/65).

#### EFFECT OF TREATMENT

A report of the effects of various kinds of treatment on the claudication index will be given in another communication. Preliminary studies indicate that repeated intravenous injections of a hypertonic solution of sodium chloride, as recommended by Silbert,<sup>5</sup> increase the claudication index.

#### DISCUSSION

There may be some difficulty in making the diagnosis of obliterating disease of the arteries, especially in cases in which the clinical manifesta-

tions are not very pronounced, e.g., when trophic lesions are absent, there is no diminution in the size of the pulses, and the roentgenograms do not show any calcification. The clinical picture in such cases may be suggestive of a great number of conditions, although a careful history enables one to exclude most of them. In some of these cases, measurement of the skin temperature may reveal a diminished response to the ablation of vasoconstrictor influences, indicating obstruction of the skin arterioles. It may be justifiable in some of these cases to assume that there is a similar occlusion of the muscle vessels. However, in many cases, early in the disease, the skin temperature may still be normal, and this might be taken to mean that the blood supply to the muscle was normal. This conclusion is, however, unwarranted. A normal response of the skin temperature to vasoconstrictor paralysis does not prove that there is a normal cutaneous circulation, as has been clearly demonstrated.<sup>14</sup> More sensitive methods can easily detect marked pathologic changes in many cases in which, as judged by skin temperature readings only, the circulation would be regarded as normal. Therefore, quite apart from the fact that it is questionable whether one may be permitted to draw conclusions concerning the blood supply to the muscles from any method of measuring the circulation to the skin, a normal response of the skin temperature is an inferior criterion of the patency and efficiency of the circulation. Indeed, there were cases in which the high claudication index which was obtained showed no relation to the severity of the trophic lesions that were present.

The ergographic method of estimating the blood supply to active muscle has the definite advantage of being able to furnish a quantitative index of the blood flow through the muscle only. After having standardized the work to be performed by each subject, and using the number of full contractions (the so-called claudication index) as a criterion, we found the indices to be above 50 in 97 per cent of the normal subjects. The indices in the limbs in which there was intermittent claudication were below 40 in 95 per cent of the cases, and in only two of thirty-eight cases were they above 40. Thus there were little overlapping and a distinct range for both the normal and abnormal extremities.

It is in the cases of early involvement that a diminished claudication index may provide valuable objective evidence of arterial obstruction. In cases of severe claudication, other signs of arterial insufficiency will make the diagnosis of arterial obstruction easy, and special investigation will not be necessary. However, it is in these cases that more information about the vascular reserve is needed in order to give a prognosis. An estimation of the latter has been made possible by recording the claudication index before and during experimental arterial occlusion in the affected limb. In cases in which the difference between these indices is very small, the prognosis has been regularly bad. In

very severe cases there may be no difference at all. A big difference, which means a considerably higher index with a free circulation, as compared with that during experimental arterial occlusion, is proof of a good vascular reserve and usually indicates a better prognosis. As a rule, patients give a history of intermittent claudication in one leg only. Despite this, the underlying pathologic condition is, in most cases, as judged by the diminished claudication index, bilateral. The condition of the "unaffected" leg can thus be assessed.

#### SUMMARY

A standardized ergographic method, by means of which a claudication index may be ascertained, has been described. This is related to the blood flow through active muscle only. In 97 per cent of the normal subjects the indices were above 50, and, in 95 per cent of the abnormal, below 40. It appears, therefore, that the circulation in a limb in which the claudication index is less than 40 is deficient, provided the muscle itself and its nerve supply are normal. Thus the degree of impairment of the circulation in the legs can be estimated. Definite relations between the degree of intermittent claudication and the claudication indices have been established. The status of the circulation to muscles can be gauged by comparing the claudication index after experimental, complete, arterial occlusion with that obtained when the arterial circulation has not been mechanically interfered with. The difference between these indices can be taken as an expression of the vascular reserve.

I wish to express my gratitude to Professor C. F. M. Saint for his interest in this work. It is with pleasure that I record my thanks to the members of the Honorary Staff of the Groote Schuur Hospital for kindly permitting me to study patients who were admitted under their care. To the many students and staff members who willingly served as subjects I extend my thanks.

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## STUDIES ON THE THIRD HEART SOUND

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**I**N A PREVIOUS paper<sup>1</sup> the suggestion was made that the third heart sound might originate in the chest wall, rather than in the heart itself. The following observations served as a basis for this suggestion. (a) A third sound had apparently never been recorded from the exposed heart of experimental animals; (b) it had not been recorded from the esophagus of man even though it could easily be recorded from the precordium of the same subject;<sup>2</sup> (c) the natural period of the human thoracic wall was of the same low frequency as the normal third sound; and (d) records of the apex beat indicate that an impact is imparted to the chest wall at the moment of the third heart sound.

Because it seemed desirable to gather more evidence for or against such a theory, the present study of registration of sounds from the exposed heart of experimental animals was undertaken.

### METHODS

Dogs, weighing 6 to 8 kilograms, were anesthetized with morphine and intravenous sodium pentobarbital. Under artificial respiration the heart was exposed by resection of the left ribs, and sounds were recorded\* directly from the surface of the left ventricle. Simultaneous records of the venous pulse, apex beat, or electrocardiogram were made. The heart sounds were transmitted to the recording apparatus by means of (a) a light wooden lever, one end of which was sewed to the myocardium and the other was cemented to a tight rubber membrane covering the open end of a large bell, (b) flexible rubber tubing sewed to the myocardium and connected to the rigidly supported microphone, the length of tubing being sufficient to absorb the movements of the heart, (c) a small shallow bell, 2.5 cm. in diameter, introduced through an opening in the parietal pericardium and held in place by sutures through the edges of the pericardium, and (d) a glass cardiometer enclosing the heart.

### RESULTS

Experiments were done on five dogs. Fig. 1A shows the sounds recorded directly from the left ventricle using a rubber tube with an

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\*All recording was done with the Stetho-Cardiette manufactured by the Sanborn Company, Cambridge, Massachusetts.

internal diameter of 3 mm. and a wall thickness of 2 mm. as a receiver; *B* shows the sounds recorded from the same animal through a tube of 6 mm. internal diameter and wall thickness of 2 mm. Record *C*, also made from the same animal, shows the sounds recorded with a bell 2.5 cm. in diameter, and simultaneous electrocardiogram. The relative sensitivity, or degree of amplification, for the records in Fig. 1 are *A* 11.5, *B* 5.5, and *C* 1. It appears that, despite increasing sensitivity, sounds are more and more attenuated by decreasing the size of the receiver applied to the heart.

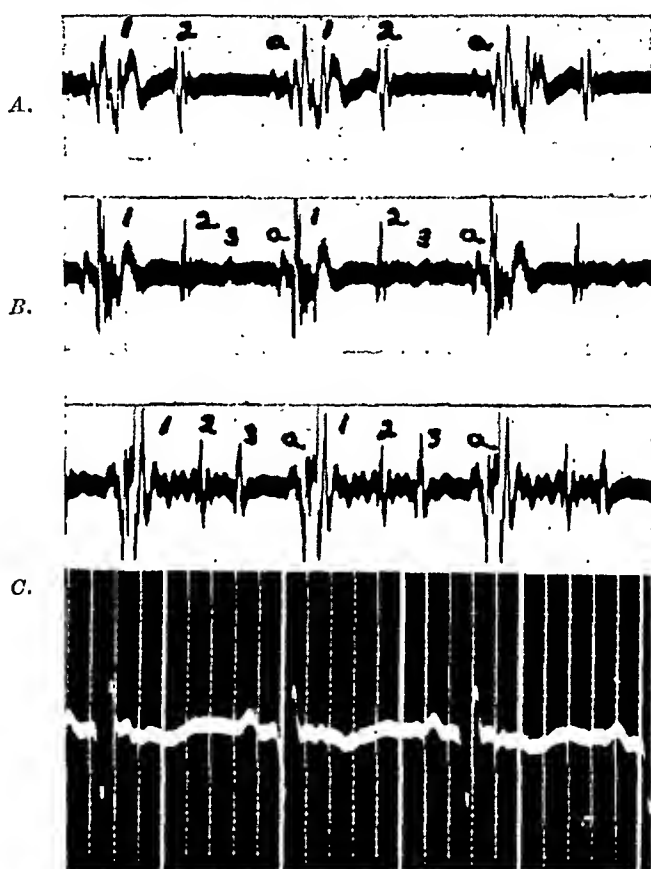


Fig. 1.—Sounds recorded directly from the surface of a dog's heart with simultaneous electrocardiogram. *A* is a record obtained when rubber tubing of small internal diameter (2 mm.) was used. Record *B* was obtained with larger sized tubing (internal diameter 6 mm.), while *C* was obtained with a shallow bell 2.5 cm. in diameter. The degrees of amplification used for *A*, *B*, and *C* were 11.5, 5.5, and 1, respectively. Note the absence of the third sound in record *A* and the progressive prominence of the third sound in records *B* and *C* as the size of the receiver is increased.

Despite very high degrees of amplification a third heart sound could never be distinguished in records made with a wooden lever or small rubber tubing sewed to the ventricle. Small vibrations at the expected moment of the third sound could usually be discerned when the larger bore tubing was used as a receiver and were prominent when recorded with the bell.

With the bell held in place only by sutures through the pericardium, uniform contact with the heart throughout the cycle could not be as-

sumed with confidence. The question naturally arose whether the impact of the beating heart against the bell might give rise to vibrations which need not be present normally.

Accordingly the following tests were made after the heart had been stopped by asphyxia. Mechanical impacts and sound vibrations were recorded from the ventricle during such manipulation of the heart as to cause it to strike the receiving bell gently. Both recording instruments were adjusted to the sensitivity which was previously used in recording from the beating heart, and records showing a mechanical impact of the same magnitude as the normal protodiastolic wave seen in the apex cardiogram were selected for study. It was found that a sound was thereby produced which was identical with the third sound in amplitude, frequency, and duration (Fig. 2*A* and *B*). The force applied to the heart to produce such an effect was so small as to preclude any interpretation other than that the sound was produced by vibration of the ventricular wall.

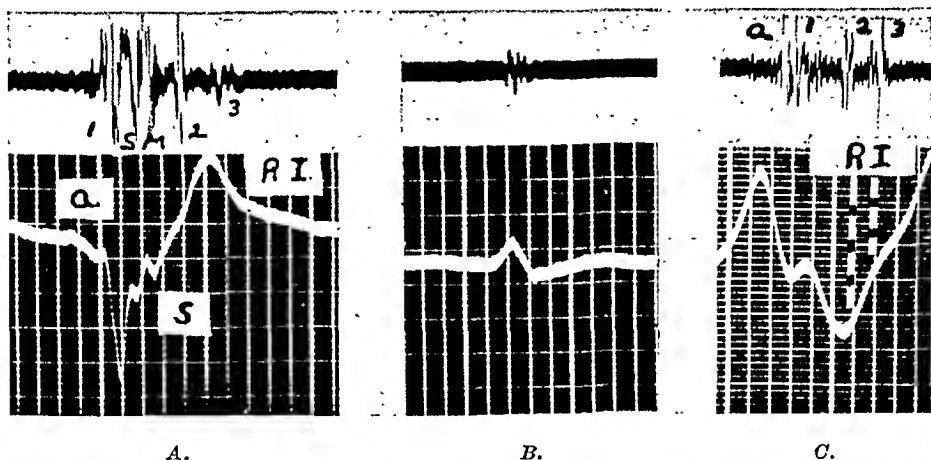


Fig. 2.—*A* shows the heart sounds and apex impulse recorded from the exposed heart of a dog after the onset of asphyxia. The heart sounds are labeled 1, 2, and 3. There is a systolic murmur which was not present in records obtained before asphyxia. In the apex cardiogram the auricular wave is labeled *a*; ventricular systole, *S*; and the rapid inflow phase, *RI*. The asphyxial record was chosen in order to make the vibration of the ventricular wall comparable with the record obtained in the quiescent heart at the end of asphyxia (*B*). *B* shows the sound (upper) and mechanical impact (lower) produced by a gentle impact of the quiescent, asphyxiated heart against the bell in the same animal from which record *A* was obtained. The sensitivities of both the sound and mechanical recorders were the same for both *A* and *B*. It will be seen that the mechanical impact is very nearly the same as the rapid inflow curve (*RI*) in *A* and that the sound produced is identical with the third heart sound. Record *C*, obtained from another animal, shows the heart sounds and ventricular volume curve, both recorded from a cardiometer in which impacts against a receiver are eliminated, and thus any possible unnatural vibrations arising from such a source are excluded. It is evident that the third heart sound continues to be present under these circumstances and occurs toward the end of the rapid filling phase (*RI*), indicated on the volume curve by the broken lines.

It was because of this observation that records were made with a cardiometer with the intent of eliminating any such unnatural vibrations. Since undoubted third sounds appeared in records obtained from the glass oncometer surrounding the heart, where impacts were certainly minimal, if not entirely eliminated, it seems clear that the sound arises in the heart (Fig. 2*C*).



When third sounds were not spontaneously present, they could always be produced by rapid intravenous infusion of saline, thereby increasing the velocity of flow during the rapid inflow phase, or by asphyxia.

#### DISCUSSION

The transmission and graphic registration of sound is a complex subject, influenced primarily by the relationship of the natural frequency and sensitivity of the apparatus to the frequency and intensity of the sound to be recorded. Due to resonating properties of recording systems, the registration of a low-pitched sound, such as the third heart sound, is best accomplished by a system of low natural frequency. Introduction into such a system of a transmitter made of stiff, insensitive material with a high natural frequency, such as wood or bamboo, will greatly attenuate low-pitched vibrations and will materially decrease the sensitivity for other frequencies as well.

Furthermore the receptor portion of the recording system serves as a cumulator of sound vibrations. Since the total energy emitted from a vibrating source is radiated in all directions, it is evident that the smaller the receiver, the less will be the proportion registered. It is admitted that this factor is probably of less importance than is the effect of introducing a relatively insensitive "high frequency" component into the system. The property of the receiver as a cumulator of sound cannot, however, be neglected.

With these principles in mind one finds little cause for wonder that a method involving the use of a relatively small solid receiver made of wood should prove inadequate for the registration of the low-frequency, low-intensity third heart sound. Unfortunately this method has been adopted frequently for the study of heart sounds recorded directly from the heart<sup>3, 4</sup> and is responsible for the erroneous deduction that, since the third heart sound was not recorded, it was not present in the heart.

Having accounted for the absence of third heart sounds previously recorded from the exposed heart of experimental animals, one can speculate as to the probable explanation for their absence in esophageal records. It was discovered in the present study that transmission by small bore tubing resulted in considerable attenuation of the first and second sounds while the third sound was eliminated entirely. In part this attenuation is due to the small size of the receiver as a cumulator of sound. Of greater importance, however, is the behavior of open receivers when they are applied to soft tissue.

Rappaport and Sprague<sup>5</sup> have pointed out that under such circumstances the tissue in contact with the receiver becomes, in fact, a diaphragm. When the receiver is large, this diaphragm has a low natural frequency and high sensitivity. Progressive decrease in the size of the

receiver results in increasing natural frequency and diminishing sensitivity of the diaphragm with consequent attenuation of all sounds but with especially adverse effects on low-frequency vibrations.

Since, of necessity, esophageal records are obtained with small bore tubing, and since the esophagus will be collapsed around the lower end of the tube, it seems probable that the same diaphragm effect may play a role here. Furthermore the degree of frictional loss in small tubing of excessive length may be considerable and will serve to further attenuate the sounds. Other factors, as yet incompletely evaluated, will perhaps further account for the absence of third heart sounds in esophageal records.

The high proportion of third heart sounds recorded from the precordium of normal subjects by Orias and Braun-Menendez<sup>6</sup> can be assigned to a method of registration which is particularly adapted to the reproduction of low-frequency, low-intensity sounds. Not only is the membrane which they used in the recording Frank capsule very loose (therefore of high sensitivity and low natural period), but also the chest piece employed was of very large size. This large receiver was designed to serve as a better cumulator of sound, which it does, but it also provides for a sensitive, low-frequency "skin diaphragm" when applied to the chest wall.

Although the exact mechanism of the production of the third sound is not known, there is general agreement that it is somehow produced by rapid filling of the ventricle during early diastole. Gibson<sup>7</sup> and Hirschfelder<sup>8</sup> were the first to suggest that the sound was created by vibration of the auriculoventricular valves toward the end of the rapid filling phase. This view has recently been supported by Lewis and Dock.<sup>9</sup> On the other hand, the South American school<sup>6</sup> vigorously supports the theory, first proposed by Ohm,<sup>10</sup> that the sound is produced by vibration of the ventricular walls. In rejecting the latter theory, Lewis and Dock wrote, "The rubbery mass of heart muscle, which from a physical standpoint seems an ideal sound deadening substance, apparently gives off no audible vibrations. Its contraction, or filling, or even its forceful impact against the chest wall contributes nothing to the heart sounds. The fact that audible vibrations can be obtained from thin strips of muscle isolated from the ventricle is of no significance, for it is easy to produce sounds with a thin rubber band but almost impossible with a rubber ball as thick walled as the heart."

This stand is untenable in view of the demonstration that the ventricular wall does give off vibrations in the audible range (Fig. 2B). It would be rash to claim that the present observations finally establish the cause of the third heart sound as due to vibration of the ventricular wall, but they do demonstrate that vibration of the ventricular wall can produce a sound comparable in every way with the normal third sound.

## SUMMARY

Heart sounds were recorded directly from the surface of the dog's heart in order to confirm or refute a previously made suggestion that the third heart sound might have its origin in the chest wall. Third sounds could readily be recorded when large, open receivers were used but not with small open receivers or when the traditional light wooden lever was used.

The physical laws bearing on the explanation for the absence of third sounds in previous records from the exposed heart of animals and from the esophagus of man have been briefly considered.

Evidence was presented to show that vibration of the ventricular wall, produced in the quiescent heart by a very feeble impact, gave rise to a sound very like the normal third sound in frequency, amplitude, and duration.

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# THERAPEUTIC PERICARDITIS BY INTRAPERICARDIAL INJECTION IN CHRONIC CORONARY INSUFFICIENCY

## A PRELIMINARY REPORT

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THE production of a sterile inflammatory reaction between the epicardium and pericardium by the direct introduction of an irritant substance into the pericardial sac has been demonstrated by many investigators. As a result of the adhesive pericarditis, a collateral vascular bed may be enhanced to such an extent that beneficial clinical effects have been observed in the treatment of coronary artery sclerosis with chronic coronary insufficiency.

The coronary arteries are normally physiologic end arteries but have anatomic facultative intercommunications. Atherosclerotic changes occur at birth and may gradually progress until death without impairing the circulation to the myocardium.<sup>1</sup> This latter might be termed physiologic coronary artery disease. Here the intimal thickening is uniform and concentric with no encroachment on the lumen. But when the process becomes eccentric, definite narrowing with diminution of blood flow occurs and pathologic coronary artery disease is present. Paradoxically, the development of a functioning collateral circulation is dependent on the extent of the disease process in the arteries. Rupture of the capillaries of the vascularized intima produces intramural hemorrhage and complete occlusion of the vessel. This obstruction to normal arterial flow through the coronary vessels is the actual stimulus to anastomotic development. If these occlusive processes are gradual, differential pressure gradients dilate previously impervious arterioles to effect an adequate collateral circulation to a potentially ischemic myocardium.<sup>2</sup> Experimentally Burchell<sup>3</sup> demonstrated that it was possible to occlude the three main coronary branches in the dog without the production of an infarct or even demonstrable cardiac disability. In the human being Blumgart and his collaborators<sup>4</sup> pointed out that, even though all three main coronary arteries were occluded, no infarctions resulted because of the development of a compensatory anastomotic circulation.

In many instances revascularization of the ischemic heart by these spontaneous processes does not suffice; therefore surgical measures have been used. Vascular channels in pericardial adhesions have been demonstrated by many studies. Moritz, Hudson, and Orgain<sup>5</sup> have shown experimentally in human hearts with adhesive pericarditis that india ink injected into the coronary arteries could be traced into the

pericardium, chest wall, and diaphragm. Thus the artificial production of a sterile adhesive pericarditis might be conducive to the development of a functioning collateral circulation to the heart. Parietal grafts to the abraded myocardium with the production of an adhesive pericarditis have been employed. Beek<sup>6, 7</sup> used a pedicled graft of the pectoralis major and burr or powdered bone meal, while O'Shaughnessy<sup>8</sup> performed a cardio-omentopexy and for his irritant used aleuronat. Thompson<sup>9</sup> did a pericardiotomy and employed tale (anhydrous magnesium silicate) to produce the adhesive pericarditis without parietal grafts.

The beneficial clinical results reported by the above-mentioned investigators have been encouraging, but the surgical procedures employed have been delicate and tedious with no little risk to a subject with an incompetent heart. If one could produce an adhesive pericarditis without pericardiotomy, much surgical trauma could be avoided. Heinbecker and Barton<sup>10</sup> were able to bring about an adhesive pericarditis experimentally in dogs by injecting a sclerosing mixture of gelatin, aleuronat, starch, glycerine, and water into the pericardial sac and, as a result of this procedure, demonstrated an adequate collateral circulation to areas of myocardium rendered ischemic by tying of branches of the coronary arteries. Beek<sup>11</sup> has mentioned the possible use of other injectable substances as sodium morrhuate. But no cases have been reported in man. It is the purpose of this paper to report two cases of pericarditis produced by the injection of an irritating substance directly into the pericardial sac of man without exposing the heart.

#### TECHNIQUE

The site selected for the pericardial puncture is the fifth left interspace just outside the apex impulse. Under aseptic conditions this area is infiltrated with 1 per cent novocaine solution. A long needle of large bore, attached to a 10 c.c. syringe filled with air, is inserted cautiously and directed medially, slightly posteriorly and cephalad. When a faint tugging sensation is perceived synchronous with the pulsations of the heart, the needle is very slightly withdrawn and 10 c.c. of air is injected under the fluoroscope. The appearance of a slight pneumocardium signifies a proper introduction of the needle into the pericardial sac, and now the sclerosing solution is injected. This consists of 18 c.c. of 5 per cent sodium morrhuate (Searle) plus 2 c.c. of iodochlor (Searle). The radiopaque character of the latter is so pronounced that it may be diluted several times and still retain its efficacy for roentgenographic studies. Thus should the needle slip outside the pericardial sac, while changing syringes, the heavier, opaque, nonirritating iodochlor would first be seen running into the pulmonary field. Following completion of the injection, the failure to visualize the opaque substance in the pulmonary fields on further roentgenographic studies is obvious evidence that it has been properly introduced into the pericardial sac.

## CASE REPORTS

CASE 1.—E. V., a white male, aged 74 years, was admitted to the Kingston Hospital Nov. 6, 1941, because of an episode of recurrent congestive heart failure. He first complained of exertional dyspnea in the fall of 1936 and shortly thereafter noted edema of the lower extremities accompanied by asthenia and occasional orthopnea. In the summer of 1937, he was confined to bed for twenty-eight days because of orthopnea, cough, marked edema of the lower extremities and slight ascites. Under a therapeutic regime of bed rest, xanthines, and small doses of digitalis, a clinical improvement was noted. Subsequently, at intervals of four to six months, he suffered with similar attacks of congestive heart failure. However, dyspnea on exertion accompanied by precordial distress has always been present.

Physical examination revealed a well-preserved, orthopneic, acyanotic white male. On examination of the fundi oculorum there was observed marked tortuosity and thickening of the retinal arteries but no hemorrhages or atrophic areas and the disc margins were clear. There was slight distention of the veins in the neck. Numerous crackling râles were heard at the bases of both lungs. The heart was moderately enlarged.  $A_2$  was greater than  $P_2$ , and except for an inconstant, very slight, soft, systolic, apical murmur no adventitious sounds were heard over the precordium. The blood pressure was 118/84 to 118/80, and the pulse rate was 78 with regular rhythm. Ascites and a marked hard edema of the lower extremities were present. A teleroentgenogram showed marked general enlargement of the cardiac silhouette. There was broadening of the shadow over the area of the great vessels with some hilar thickening and accentuation of the lung markings. Except for obliteration of the left diaphragm and costophrenic angle the periphery of both lung fields was clear. An electrocardiogram revealed occasional premature ventricular systoles, left axis deviation, and inverted T waves in Lead I and the precordial lead (IVF). Chemical examination of the blood and urine revealed nothing significant. Microscopic examination of the urine revealed a moderate number of pus cells. There were 74 per cent of hemoglobin in the blood (15.6 Gm. equals 100 per cent), 4,260,000 erythrocytes per cubic millimeter, and 7,400 leucocytes per cubic millimeter of which 72 per cent were polymorphonuclear neutrophils. Serologic tests revealed no evidence of syphilis.

A diagnosis was made of arteriosclerotic heart disease with coronary arteriosclerosis and chronic coronary insufficiency, cardiac hypertrophy with diffuse myocardial fibrosis, and congestive heart failure. Therapy consisted only of bed rest and small doses of diuretin (10 gr. twice daily for five days). On Nov. 8, 1941, an unsuccessful attempt to introduce 5 per cent sodium morrhuate into the pericardial sac produced no ill effects. This was not done with the radiopaque substance under the fluoroscope, and apparently the solution was injected into the left pulmonary field. The temperature rose to 101.2° F. for only twenty-four hours, and roentgenograms revealed no pulmonary changes. Adventitious sounds were not heard over the precordium, and the patient made no complaints.

On Nov. 11, 1941, a pericardial injection was successfully performed by the above-described technique. The patient complained only of slight temporary pain in the left side of the chest and the left arm. Within a few hours the temperature rose to 103.2° F. and was accompanied by a leucocytosis of 14,800 with 89 per cent of polymorphonuclear leucocytes. A faint, localized pericardial friction rub over the apical area was not heard until eighteen hours later. This soon increased in intensity and distribution and persisted until eight days later at which time both the leucocyte count and temperature had receded to normal levels. The blood pressure and pulse rate did not vary appreciably. On November 16, the peripheral edema, ascites, and dyspnea were no longer present; and surprisingly enough immediately after the operation the patient enjoyed bathroom privileges, smoked cigars, and felt entirely comfortable. Complaints were

referred only to the genitourinary system because of prostatic disease. Roentgenographic studies revealed a clearing of the disturbance at the base of the left lung. Electrocardiograms did not differ significantly from the one reported until early in the third week when T wave negatively appeared in Lead II and became more pronounced in Leads I and IVF.

CASE 2.—E. B., a white female, aged 74 years, was admitted to the Kingston Hospital on Nov. 21, 1941, because of congestive heart failure. The patient had suffered from recurrent bouts of congestive heart failure for the past three years but first noted exertional dyspnea and precordial distress about five years ago. Her symptoms were usually alleviated by a combination of xanthines and very small doses of digitalis. However, the last attack had not responded to this therapy, and hospitalization was advised.

Physical examination revealed a very dyspneic, apprehensive woman. There was slight cyanosis of the lips, ears, and fingers, and the veins of the neck were markedly distended. Examination of the fundi oculorum revealed no significant retinopathy. At the bases of the lungs there was slight impaired resonance with many crackling râles. The heart was moderately enlarged, but no adventitious sounds were heard on auscultation.  $A_2$  was greater than  $P_2$ , and the blood pressure was 150/82 to 150/80. A markedly enlarged, tender liver was associated with a moderate ascites. The lower abdominal wall and lower extremities were edematous; the edema was of a soft, pitting variety.

Electrocardiographic studies demonstrated nodal rhythm with an occasional premature ventricular systole and low voltage in all leads (0.2 to 0.3 millivolts). The venous pressure in the right arm was 24.5 cm. of water. A roentgenogram of the chest revealed some hilar thickening with accentuation of lung markings, slight bronchial infiltration, and some haziness over both bases. The cardiac shadow was enlarged. Chemical analyses of the blood were not significant. Serologic tests for syphilis were negative. The erythrocytes numbered 4,960,000 per cubic millimeter of blood with 85 per cent of hemoglobin (15.6 Gm. equals 100 per cent), and the leucocytes numbered 5,950 per cubic millimeter of which 52 per cent were polymorphonuclear neutrophils. Examination of the urine revealed a slight trace of albumin, 5 to 8 pus cells, and a few fine and coarse granular casts per low-power field.

A diagnosis was made of arteriosclerotic heart disease with coronary artery sclerosis and chronic coronary insufficiency, cardiac hypertrophy with diffuse myocardial fibrosis, and congestive heart failure. Therapy consisted only of bed rest and barbiturate sedation.

On November 23, a successful injection into the precordial sac was performed. Within twenty minutes a very loud, harsh pericardial rub was heard over the entire precordium. Curiously enough, the rub completely disappeared at the end of one hour. Eighteen hours later there was a mild febrile reaction (100.8° F.) accompanied by a slight leucocytosis which persisted for four days and was associated with a slight pericardial quality to the heart sounds. At no time did the early electrocardiograms reveal elevation of the S-T junction but rather absent positive deflection in the precordial lead (IVF) together with a diphasic T wave. The blood pressure and pulse rate did not vary significantly. The only untoward symptom was vomiting. This appeared shortly after the injection and continued at intervals for five hours, but was believed to be due to an error in diet plus sensitivity to morphine, which had been administered preoperatively. The patient's subsequent clinical improvement was remarkable. Five days after this procedure a slight ascites was the only residual manifestation of her severe congestive heart failure. The patient stated she breathed more easily and felt generally better. She was discharged twelve days after her treatment at which time an electrocardiogram showed  $T_1$  and  $T_2$  to be inverted as was the T wave in the precordial lead (IVF).

## COMMENT

In 1932, Hudson, Moritz, and Wearn<sup>12</sup> demonstrated the rich potential extracardiac coronary circulation to the human heart, and a contemporary publication mentioned that this extrinsic collateral circulation was augmented by pericardial adhesions. In addition Mautz and Beck<sup>13</sup> reported that the intercoronary collateral circulation was enhanced by these adhesions. Subsequent experimental and clinical observations have shown the efficacy of a collateral vascular bed to the myocardium brought about by an adhesive pericarditis. Experimentally in rabbits we have produced an adhesive pericarditis by exposing the pericardial sac and injecting a solution of 5 per cent sodium morrhuate plus a small amount of iodochlor with no deleterious effects.

A similar solution injected without exposure into the pericardial cavity of two patients suffering with arteriosclerotic heart disease and chronic coronary insufficiency has produced a clinical pericarditis without interference of the heart action. The clinical manifestations of pericarditis were fever, leucocytosis, and pericardial friction rub, and, although S-T segment alterations usually observed in acute pericarditis were absent, later electrocardiograms showed T-wave inversions suggestive of a healing stage in acute pericarditis. Since the work of Burchell and his collaborators<sup>14</sup> seems to indicate that such changes are caused by a subpericardial myocarditis, we may accept these T-wave alterations as evidence that the epicardial barrier between intercoronary and extracoronary circulation has been removed. The early clinical improvement observed might be caused by the rapid opening of intercoronary communications.<sup>15</sup> However, the permanency of the beneficial effects of this attempted revascularization of the myocardium will also be dependent on the extracardiac anastomoses. This is doubted by some investigators<sup>3</sup> who have been unable to find supportive evidence that vascularized tissue grafts play a useful function in the re-establishment of coronary circulation following experimental occlusion of the coronary arteries. Certainly further clinical observation and histologic studies are necessary in my limited number of cases. Appreciating the paucity of material at hand, I suggest this method of producing a sterile, adhesive pericarditis in the treatment of myocardial ischemia in man in the hope that others may further investigate its possibilities.

## CONCLUSION

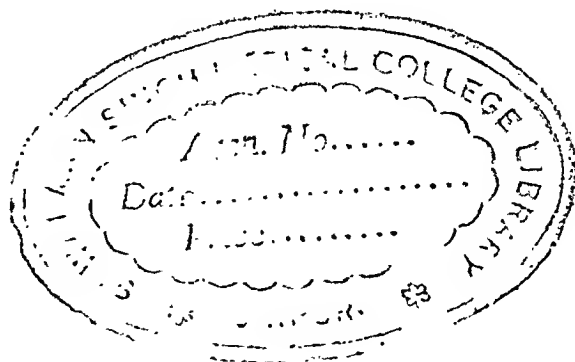
A pericarditis, the result of injecting an irritating substance into the pericardial sac, has been employed in the treatment of two cases of chronic coronary insufficiency with apparent beneficial results.

I am deeply grateful to J. Spottiswood Taylor, M.D., Director of the Kingston Laboratory, and Mr. William Goodrich and Mr. Fred Smith of the Staff for their technical assistance in the experimental work.



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## APICAL DIASTOLIC MURMURS WITHOUT MITRAL STENOSIS

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THE occurrence of a rumbling diastolic murmur at the apex, exclusive of the Austin Flint murmur, unaccompanied by organic mitral stenosis, has long been known. As early as 1894 Fisher<sup>1</sup> published five such cases. The following year Phear<sup>2</sup> reported two cases and collected nineteen others from the literature. From the writings of Hirschfelder,<sup>3</sup> Flint<sup>4</sup> and Cabot<sup>5</sup> it is evident that they were cognizant that apical diastolic murmurs could occur in enlarged hearts without mitral stenosis. In 1923, Wood and White<sup>6</sup> reviewed twenty necropsy records of patients with marked cardiac hypertrophy with normal valves. Four of these had diastolic murmurs at the apex. In 1929, Bach and Keith<sup>7</sup> presented a similar case. Sheldon,<sup>8</sup> McKee,<sup>9</sup> Schlesinger<sup>10</sup> and Taussig<sup>11</sup> pointed to the presence of a diastolic murmur in the early stages of rheumatic disease before the appearance of mitral stenosis. In 1933, Gunewardene<sup>12</sup> pointed out that a presystolic or diastolic murmur with clinically marked cardiac dilatation often occurs in children with ankylostoma infection. With treatment the heart returned to normal size and the murmurs disappeared. Bland, White, and Jones<sup>13</sup> in 1935 reported a series of 100 patients dying with rheumatic heart disease. Clinical mitral stenosis was diagnosed in sixty-eight cases while anatomic stenosis was present in only twenty-three. This was re-emphasized by the authors in 1936.<sup>14</sup> Yet Thompson and Levine<sup>15</sup> from a clinical and pathologic correlation report a high degree of accuracy in the diagnosis of mitral stenosis, either when it occurs alone or when it is associated with other valvular lesions.

We have studied clinically five patients with diastolic murmurs at the apex who showed no mitral stenosis pathologically. In view of the general belief that the mild or low rumbling diastolic murmur at the cardiac apex (in the absence of aortic regurgitation) signifies organic mitral stenosis, we present these cases.

### CASE REPORTS

CASE 1.—T. M., a 15-year-old white female, entered Michael Reese Hospital on March 4, 1937. She had had frequent attacks of tonsillitis, and one year before entry she had her first attack of polyarthritis, at which time rheumatic heart disease was diagnosed. Because of persistent fever, orthopnea, and precordial pain, she was referred to the hospital. The heart was enlarged and  $P_2$  was accentuated. All

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of the medical staff agreed at various times during her stay that there were systolic and diastolic murmurs at the apex, some calling the latter mid-diastolic and others presystolic. Likewise all agreed that there was a diastolic thrill at the apex (some calling it presystolic). The x-ray and fluoroscopic examination confirmed the presence of an enlarged heart and also showed the left auricle appearing within the shadow of the right auricle. The liver edge was palpable, 1 fingerbreadth below the costal margin. She improved, was sent home after two months, and was followed in the outpatient clinic for a few months. She was referred back to the hospital on Aug. 7, 1937, because of dyspnea and orthopnea. All during this period the heart findings were the same as above. On this admission, in addition to the apical findings, one observer heard at the third and fourth left interspace, a soft diastolic murmur which subsequently disappeared. The blood pressure at this time was 108/66 mm. Hg. Subsequent blood pressures ranged from 122 to 100 systolic and 94 to 64 diastolic. She improved after a six months' stay, was home for five months, and re-entered in severe heart failure. Again all observers agreed that there was a double murmur at the apex with a diastolic thrill. The blood pressure varied from 126/94 to 92/60. After seven more months the patient died in heart failure.

*Post-Mortem Examination of the Heart.*—The heart was markedly enlarged to the right and left; it weighed 400 Gm. There were firm adhesions between the pericardium and epicardium, in addition to some fine easily separated strands. All chambers of the heart were dilated. The endocardium of the left auricle adjacent to the inferior leaflet presented multiple coarse corrugations and wrinklins. The mitral orifice measured 10.4 cm. in circumference. The line of closure of the leaflets of the mitral valve showed minimal to moderate thickening with a row of fine verrucae. The corresponding chordae tendinae were moderately thickened, in a few spots fused, and somewhat shortened. The circumference of the aortic orifice measured 7 cm. The cusps of the aortic valve were slightly thickened, and shortened, and minimally adherent at the commissures. The circumferences of the tricuspid and pulmonic valves measured 11 and 8 cm., respectively. The corresponding valves presented no gross changes. On section the myocardium was greyish red and parboiled in appearance. Microscopically the myocardium revealed swollen and poorly stained muscle fibers. There was a diffuse, loose network of fine fibrillar connective tissue separating small groups of muscle fibers. Many areas presented a perivascular, markedly eosinophilic, fibrillar substance with particles of swollen collagen and a moderate distribution of lymphocytes, fibroblasts, and plasma cells. An occasional Aschoff body was noted. The diagnosis was (1) old endocarditis of the mitral and aortic valves with insufficiency of their orifices (aortic minimal, mitral moderate), (2) old mural endocarditis, (3) acute verrucous endocarditis of the mitral valves, (4) acute and old rheumatic myocarditis, (5) old pericarditis, (6) chronic passive hyperemia of the lungs, liver, spleen, kidneys, and gastrointestinal tract, (7) fatty degeneration of the liver, (8) fibrosis of the spleen, (9) ascites, and (10) peripheral edema.

CASE 2.—J. K., a female child, was first seen on Dec. 27, 1931, at the age of 5.5 years and was followed for a period of six years. She had scarlet fever at the age of 3 years. Her first entry into Sarah Morris Hospital was because of chorea, and during her course she had multiple such attacks. On her first admission a soft systolic murmur was heard at the apex with an accentuated first sound. The heart was not enlarged. On her second and third admissions at the age of 8, definite harsh systolic and diastolic murmurs were heard at the apex, coupled with a mitral configuration of the heart on x-ray examination, and a right axis shift in the electrocardiogram. She was not in failure, but periodically continued to run a febrile course. On her readmission at the age of 11, the diastolic murmur was questionable, although the other findings were the same. On her final admission she was in

heart failure. Systolic and diastolic murmurs were again heard at the apex, and electrocardiogram and x-ray examination were as previously. Hoarseness developed which was interpreted as being due to left auricular pressure on the recurrent laryngeal nerve. The patient gradually became worse and died in marked congestive failure.

*Post-Mortem Examination of the Heart.*—The heart was markedly enlarged to the right and left and weighed 300 Gm. On the epicardium covering the left base anteriorly there was an irregular, white streaked plaque. The tricuspid orifice measured 12 cm. in circumference. The valve leaflets presented numerous firm, pinkish-grey excrescences. The mitral orifice measured 13 cm. in circumference, and similar excrescences were present on the line of closure of the inferior leaflet. The edges of both leaflets of this valve had a somewhat scalloped appearance. The aortic and pulmonic orifices measured 7 and 8 cm. in circumference, respectively, and the corresponding valves were normal. All cardiac chambers were markedly dilated. The myocardium was markedly flabby, pale, reddish brown, and distinctly parboiled in appearance. Microscopic examination revealed a moderate perivascular fibrosis throughout the myocardium. In some areas there were accumulations of lymphocytes and endothelial leucocytes. The muscle fibers were larger than normal, and the intercalated discs were very prominent. No Aschoff bodies were noted in the myocardium. The endocardium revealed occasional foci of lymphocytes and fibroblastic cells. The diagnosis was (1) chronic myocarditis, (2) old endocarditis of the mitral valve with acute verrucous endocarditis of the tricuspid and mitral valves, (3) moderate hypertrophy and marked dilatation of the heart, most marked in the right ventricle, (4) chronic peri- and endarteritis of the smaller branches of the pulmonary artery, with organized and organizing thrombi and pulmonary infarcts, (5) chronic passive hyperemia of the lungs, liver, and spleen, (6) left hydrothorax, ascites, and peripheral edema, (7) recent and organizing bronchopneumonia, (8) subacute splenic hyperplasia, and (9) cloudy swelling of the kidneys.

CASE 3.—E. L., a 25-year-old white female, entered Michael Reese Hospital on July 15, 1921, in the puerperium of a complicated labor, complaining of chills, fever, and marked weakness. She gave a previous history of scarlet fever. Physical examination at this time revealed râles in the lungs with high fever and no enlargement of the heart. A soft, blowing nontransmitted, systolic murmur was heard at the apex. The patient's course was septic for four months during which time the heart size gradually increased. With the disappearance of the sepsis the heart remained enlarged. The patient was discharged on Dec. 19, 1921, five months after entry. A diagnosis of post-infectious myocarditis was made. Seven years later the patient was seen in heart failure, with marked cardiac enlargement and auricular fibrillation. No definite murmurs were heard at this time. The blood pressure was 124/80. A half year later a pulsating, inguinal mass was discovered, and a questionable diastolic murmur at the apex was heard. A diagnosis of arteriovenous aneurysm was now made. Four years later the patient was again seen in right heart failure and auricular fibrillation. This time various observers described a loud, rough, long drawn out, crescendo, presystolic murmur, or diastolic murmur at the apex. A diagnosis was now made of rheumatic heart disease with mitral stenosis and insufficiency. In two subsequent bouts of heart failure two and three years later no distinct murmurs could be heard because of the weak and irregular heart action. The blood pressures on the two admissions were 110/70 and 100/70, respectively. In her last attack, however, six months later, a presystolic murmur was again heard. The patient died in right heart failure on March 19, 1936. The final diagnosis was arteriovenous aneurysm, and mitral insufficiency and stenosis.

*Post-Mortem Examination.*—Two arteriovenous aneurysms were found involving the right iliac and right external pudendal veins and arteries, respectively. The

heart was tremendously enlarged and filled three-fourths of the chest cavity. It weighed 425 Gm. The enlargement was due mostly to dilatation of the right auricle and ventricle, although the left auricle and ventricle were also moderately dilated. The right and left ventricular walls measured 0.3 to 0.4 cm. and 1 cm., respectively. The circumference of the mitral valve was 10 cm. The line of closure of the leaflets was somewhat thickened, and the chordae were slightly shortened. Several small verrucae were present on the inferior leaflet. The tricuspid orifice was markedly dilated, but its valve showed no change. The orifices and leaflets of the aortic and pulmonic valves were normal. Several small areas of fine granularity were present on the pericardium. The endocardium showed no gross changes. Histologically the fibers of the myocardium were swollen and their cytoplasm was pale stained with obscure striations. The fibers of the right ventricle were somewhat enlarged. The perivascular connective tissue was moderately increased in amount and occasionally infiltrated with round cells. The walls of the arteries were slightly thickened and hyalinized. The epicardium was thickened and edematous with many round cells embedded in fibrin. The diagnosis was (1) marked hypertrophy and dilatation of the right ventricle and auricle, (2) marked dilatation of the tricuspid orifice with insufficiency of the valve, (3) acute verrucous endocarditis superimposed on a healed endocarditis of the mitral valve with questionable insufficiency, (4) acute serofibrinous pericarditis, (5) arteriovenous aneurysms involving the right iliac and right external pudendal veins and arteries, (6) marked chronic passive hyperemia of the liver, spleen, and kidneys, and (7) bilateral hydrothorax, ascites, and peripheral edema.

CASE 4.—P. D., a 21-year-old white male, entered Michael Reese Hospital on Feb. 17, 1933, with a history of progressive weakness, dyspnea, and mild precordial pain of four months' duration. He had never suffered from rheumatism, scarlet fever, chorea, or tonsillitis. Physical examination at time of admission revealed enlargement of the heart to the right and left on percussion. Apical murmurs were described by some as presystolic and systolic, and by others as systolic and rumbling diastolic. A soft diastolic murmur was heard over the aortic area and in the third and fourth left interspace by some, and not heard by others. The liver was just palpable, while the spleen was distinctly palpable. The arterial blood pressure on admission was 102/40. The temperature was 100° F., and the pulse rate was 104. A diagnosis of rheumatic heart disease with mitral stenosis and insufficiency and possible aortic insufficiency was entertained, with subacute bacterial endocarditis to be ruled out. The patient was in the hospital for six weeks. A rumbling apical diastolic murmur continued to be heard, while the diastolic pressure rose to 60 mm. The temperature fell to normal; the patient improved, was up and about, and was discharged on April 3, 1933, on a regime of restricted activities and on digitalis. He was readmitted to the hospital on April 13, 1934, with sudden sharp severe pain beneath the left lowermost ribs, accompanied by nausea, vomiting, and shortness of breath. Physical examination revealed enlargement of the heart with auricular fibrillation. This time, however, no apical murmurs were heard. A systolic and diastolic thrill, or murmur, or both were heard and felt over the pulmonic area by various observers. The liver was now distinctly palpable while the spleen was not. The arterial blood pressure was 100/70. The patient died after four days in congestive heart failure.

*Post-Mortem Examination of the Heart.*—The heart was markedly enlarged to the right and left and weighed 550 Gm. All chambers were dilated, especially the left ventricle. The valvular apparatus presented no abnormality. The myocardium was soft and flabby throughout. On section its normal architecture was obscured, its cut surface being shaggy, granular with numerous minute, irregularly demarcated, pinkish-grey areas and streaks. Recent mural thrombi were present in the left

ventricle and the right auricle. The pericardium showed no changes. Microscopic examination revealed a diffuse moderate new formation of connective tissue containing a moderate number of lymphocytes and endothelial leucocytes. In addition there was a distinct perivascular infiltration of similar cells. Only an occasional section presented a few larger cells with distinct basophilic cytoplasm and spider web-shaped nuclei. An occasional such cell contained two nuclei. These groups of cells could not definitely be interpreted as Aschoff bodies. Other fields showed a moderate amount of red staining material engulfing cellular elements. The muscle fibers throughout showed marked degenerative changes. The endocardium in many places was markedly thickened and infiltrated with lymphocytes and endothelial cells. The pericardium showed no histopathologic change. The diagnosis was (1) subacute and chronic myocarditis, (2) marked hypertrophy and dilatation of the heart (right and left ventricle), (3) mural thrombi in the right auricle and left ventricle, (4) recent infarct of the left kidney, (5) old infarct of the spleen, (6) multiple emboli in branches of the pulmonary artery, (7) recent infarcts of both lungs, (8) chronic passive hyperemia of the lungs, liver, spleen, and kidneys, and (9) hydrothorax, hydropericardium, ascites, and peripheral edema.

CASE 5.—D. D., an 8.5-year-old boy, entered Sarah Morris Hospital on June 10, 1938. One year before entry he had an attack of rheumatic fever. Although joint phenomena disappeared within a few weeks, he remained in bed for five months because of cardiac findings. He was on graded activity and had no cardiac symptoms until two months before entry, when he had the measles. Subsequent to this he progressively developed dyspnea, orthopnea, cough, and peripheral edema, necessitating his entry into the hospital. Physical examination on admission revealed the heart to be enlarged to the left and right. Systolic and diastolic murmurs were heard at the apex. The liver was palpable 5 fingerbreadths below the costal margin, and there was peripheral edema. The blood pressure was 110/70, and the pulse rate was 100. A diagnosis of old rheumatic endocarditis with mitral insufficiency and stenosis, with an acute exacerbation, was made. During his two-week stay in the hospital the diastolic murmur disappeared. The patient's course was rapidly downhill, and he died in heart failure on June 30, 1938.

*Post-Mortem Examination of the Heart.*—The heart was distinctly enlarged and weighed 300 Gm. The right and left ventricles were dilated. The left auricle was also thickened. The circumferences of the valvular orifices measured as follows: Tricuspid, 8 cm.; pulmonic, 6 cm.; mitral, 9.9 cm.; and aortic, 5.8 cm. The leaflets of the mitral valve were moderately thickened, with a fine scalloping of the edges. The corresponding chordae tendineae were shortened and in spots fused. A row of minute fibrinous excrescences were present on the line of closure of the inferior leaflet. The aortic cusps were somewhat shortened and thickened. The tricuspid and pulmonic valves showed no gross changes. The epicardium presented a fine granularity over the anterior wall of the right ventricle. The endocardium was normal. Histologic examination of the myocardium revealed a considerable amount of fibrillar connective tissue which in some regions was quite cellular. Clear fat spaces were also noted between the muscle bundles. No Aschoff bodies were in evidence in the specimen examined. The striations of the muscle fibers were indistinct. The diagnosis was (1) acute verrucous endocarditis superimposed on old endocarditis of the mitral valve with insufficiency of the valve, (2) chronic valvulitis of the aortic valve with possible slight insufficiency, (3) fibrosis and cloudy swelling of the myocardium, (4) hypertrophy and dilatation of the right and left ventricles and left auricle, (5) acute fibrinous pericarditis, (6) chronic passive hyperemia of the lungs, liver, spleen, and kidneys, and (7) slight hydrothorax, hydropericardium, and hydroperitoneum.

## DISCUSSION

In all of these patients, at one time or another, a diastolic murmur was heard at the apex. In most instances it was rumbling in character. In four cases it was not always present. In one case it was accompanied by an apical thrill. In none of these cases at autopsy was there any evidence of anatomic mitral stenosis. As a matter of fact, in three cases the mitral orifice actually exceeded the tricuspid orifice in circumference or was proportionally enlarged. In two cases there was minimal anatomic evidence of aortic regurgitation. The accompanying blood pressures and anatomic evidence indicated that the insufficiency was too small to produce an Austin Flint murmur. In the case with the isolated myocarditis there was no anatomic lesion at the mitral valve. In the other hearts, there was either acute or subacute verrucous endocarditis or older endocarditis with regurgitation.

As to the etiology of the murmurs, various theories have been suggested. Fisher,<sup>1</sup> Phear,<sup>2</sup> Wood and White<sup>6</sup> and Gunewardene<sup>12</sup> suggested that a relative mitral stenosis was produced by a marked increase in size of the left ventricle due to dilatation. Phear,<sup>2</sup> and Wood and White<sup>6</sup> in addition stressed the necessity of forcible heart action in the production of the murmur. Bland, White, and Jones<sup>13</sup> further suggested that vibrations set up by the diastolic filling of a capacious cavity with relaxed and relatively atonic walls might be responsible for the murmur. Kerr<sup>16</sup> believed that the apical diastolic murmurs heard in the acute stage of rheumatic fever, in severe anemias and leucemias, are due to relative insufficiency of the pulmonary valve. This he<sup>18</sup> explained might result from a mechanical impingement of the dilated pulmonary ring on the mitral ring leading to narrowing of the latter. Sheldon<sup>8</sup> suggested that the murmur was produced when the ventricle sucked blood from the auricle through a thickened or stiffened mitral valve during diastole. Fishberg<sup>17</sup> attributed this murmur to early rheumatic changes in the mitral leaflets which diminish their flexibility so that blood currents set them in audible vibrations.

The common anatomic characteristics in our series are (1) marked dilatation of all the chambers of the heart and (2) myocardial lesions (either an active myocarditis or fibrosis). The absence of any anatomic findings of the mitral valve in one heart definitely refutes Sheldon's theory. Against Kerr's theory is the absence of any marked dilatation of the pulmonary orifice at post-mortem examination. In addition, in the terminal stages, when we should expect the pulmonary insufficiency to be greatest the murmur in several cases disappeared. The anatomic evidence of dilatation of the left auricle and ventricle and the myocardial disease suggest that the most plausible explanation is the production of a relative mitral stenosis by the dilatation of the adjacent chambers. The disappearance of the murmur terminally in two cases suggests that

a certain amount of myocardial power is necessary for the production of the murmur as Phear suggested. The possibility of vibrations of a capacious cavity of course cannot be excluded. We would tend to minimize the possibility of a relative aortic regurgitation producing an Austin Flint murmur, for it is the general consensus of opinion that it requires considerable aortic regurgitation to produce this murmur<sup>15</sup> and in none of our cases were the signs of a marked aortic insufficiency present. The possibility that a previously present mild mitral stenosis was obliterated by the terminal dilatation of the orifice is excluded, for this could not be present in the isolated myocarditis without mitral disease. Fishberg's suggestion certainly could not explain the murmurs arising in our case of isolated myocarditis or in Gunewardene's cases.

Clinically, certain criteria have been accepted as aids in the diagnosis of mitral stenosis. In all the cases reported there was other evidence which supported the presence of stenosis, in addition to the auscultatory findings. A definite diastolic thrill was present in one case.  $P_2$  was accentuated in all cases. Auricular fibrillation was present in two cases. Electrocardiographic changes, such as enlarged P waves, right axis shift or ventricular preponderance, were present in all cases. Fluoroscopic and roentgenologic examination always showed left auricular enlargement. In two of our cases the left auricle formed part of the right heart border, an accepted view of marked left auricular enlargement. In one of our cases hoarseness developed which has been described in rare cases of mitral stenosis.

Certain circumstances will aid in avoiding an incorrect diagnosis of mitral stenosis. In the presence of marked cardiac enlargement, especially if the case has been followed for only a short time, there should be a hesitancy in making a definite diagnosis of mitral stenosis. It cannot be overemphasized that stenosis usually takes several years to develop. Finally, as in Cases 1 and 2, there are patients with rheumatic heart disease who never fully recover from their initial attack or are constantly being reinfected at short intervals. In such patients a diastolic murmur may appear, as it frequently does in acute rheumatic fever, and it may persist for years. In this type of case the probability of the absence of mitral stenosis should be considered.

The occurrence of such cases is probably more frequent than is generally believed. Bland, Jones, and White<sup>14</sup> have reported a series of eighty cases in which diastolic murmurs have been present for years only to disappear and never reappear. In our report five cases are reported in which complete post-mortem examination demonstrated conclusively the absence of mitral stenosis.

#### CONCLUSION

Five cases of clinically present apical diastolic murmurs unaccompanied by mitral stenosis are reported. These cases again demonstrate



that, in the presence of dilated heart chambers, apical diastolic murmurs may be heard in the absence of mitral stenosis or marked aortic regurgitation. The clinical circumstances of this occurrence are discussed. Anatomic evidence is presented indicating that a relative mitral stenosis produced by dilatation of the left auricle and ventricle is responsible for the murmur.

We are indebted to the several physicians of Michael Reese Hospital in charge of these patients for permission to report the cases, to Dr. O. Saphir for reviewing the anatomic findings, and to Dr. L. N. Katz for suggestions during the study and in the preparation of the report.

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# EVALUATION OF THE LOCAL VASODILATOR EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL) BY IONTOPHORESIS

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THE production of local hyperemia using choline derivatives by iontophoresis has received considerable clinical trial in recent years. Of the compounds examined, acetyl-beta-methylcholine chloride (mecholy) has been found to be the most desirable preparation for this purpose.<sup>1, 2</sup> The basis for the belief that this drug has a local vasodilating effect, however, rests primarily upon such indirect proof as the redness of the part, an elevation of skin temperature<sup>3a</sup> and an observed increase in the rate of capillary flow.<sup>3b</sup> The only direct and quantitative measurements were performed by Montgomery and his associates,<sup>4</sup> who found that a significant increase in the rate of blood flow was elicited in the hand and that this persisted for some time after the termination of the procedure.

Since it has been shown that the response of the blood vessels to various types of stimuli is different in the hand from that in other portions of the extremities,<sup>5</sup> it was considered of interest in the present investigation to obtain a more general evaluation of the peripheral vasodilating effect of mecholy\* iontophoresis by studying the changes produced in the forearm, leg, and foot.

## METHOD

The experiments were performed upon nine normal subjects. In view of the constancy of the results, a larger series was not considered necessary. Each person, however, was used repeatedly in an attempt to determine the relative role of the density and duration of the current in the production of the blood flow change. In all, the forearm was studied seventeen times, the leg, eight times, and the foot, five times. Blood flow readings, in cubic centimeters per minute per 100 c.c. of limb volume, were obtained by means of the venous occlusion plethysmographie method, the technique being identical in all respects with that previously reported.<sup>6</sup> The water in the plethysmograph (bath temperature) was either 32° or 45° C. In a number of instances, two portions of different extremities were studied simultaneously.

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As in the study by Montgomery and his associates,<sup>4</sup> the plethysmograph, filled with a 0.2 per cent aqueous solution of mecholyl, was utilized as the positive electrode for iontophoresis, while the negative electrode consisted of an asbestos-covered metal sheet which was thoroughly saturated with warm water and applied to the anterior surface of the abdomen. Special precautions were taken to insulate all metal portions of the plethysmograph which might come in contact with the extremity and thus cause an electrical burn. Current densities of 5 to 15 milliamperes, obtained from a 45-volt "B" battery, were used for periods of ten to twenty minutes. In those instances in which the vasodilating effect of the galvanic current alone was studied, the plethysmograph was filled with physiologic saline instead of a 0.2 per cent solution of mecholyl. In the experiments in which two different extremities were placed in plethysmographs, one machine was filled with water and no current was applied, while the other was utilized in the production of mecholyl iontophoresis in the manner described above.

At least fifteen to twenty blood flow readings were obtained, first in a control period of twenty to thirty minutes, then during the time the current was applied, and finally in the one- to two-hour period following. In those instances in which the effect of varying the intensity or duration of the current was studied, the blood flow readings were utilized in the construction of a graph. By means of a planimeter, the magnitude of the excess blood flow, over and beyond the previously determined basal level, was calculated separately for the period of iontophoresis and for that immediately following. By this means an accurate comparison could be made of the magnitude of the blood flow change elicited by each set of experimental conditions.

Besides blood flow studies, blood pressure and pulse rate readings were obtained repeatedly before, during, and after the period of iontophoresis. All objective and subjective symptoms were likewise recorded.

#### RESULTS

*Forearm.*—In every instance, mecholyl iontophoresis produced a significant augmentation in the rate of blood flow through the forearm. This began within two minutes after the onset of the procedure and quickly reached a maximum which was maintained for the remainder of the treatment period. On termination of the current, there was a gradual decrease, and a return to the level of the control blood flow within thirty-five to ninety-five minutes afterward (an average of fifty minutes). The findings in Fig. 1B are typical of the response. The average maximal increase in flow was 2.5 times the basal level. The application of the galvanic current alone, in the case of the plethysmograph filled with physiologic saline, produced only a very slight increase in forearm blood flow. In those experiments in which two dif-

ferent extremities were studied simultaneously, with only one being subjected to iontophoresis, the other never demonstrated any increase in blood flow.

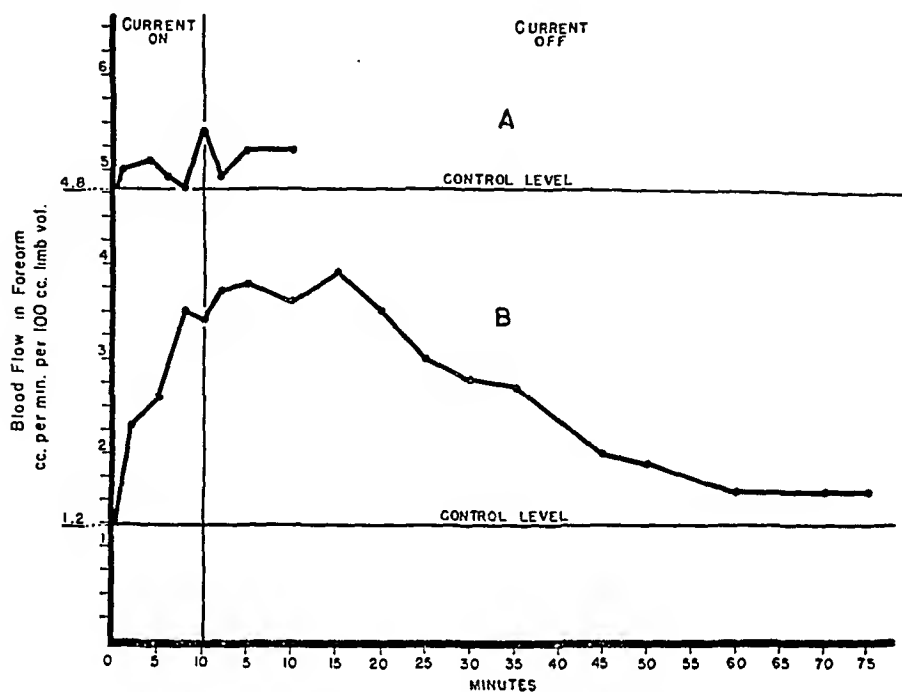


Fig. 1.—Effect of varying the bath temperature upon the blood flow response to a ten-minute period of mecholyl iontophoresis (current density, 15 milliamperes). A, Bath temperature, 45° C.; control flow in forearm, 4.8 c.c. per minute per 100 c.c. limb volume. B, Bath temperature, 32° C.; control flow in same forearm, 1.2 c.c. Room temperature was 27° C.

*Leg.*—The vasodilator effect in the leg was less than that in the forearm, the average maximal increase in blood flow being 1.8 times the control flow. The response began within three minutes after the current was turned on, and the increased flow continued for from twenty-one to forty minutes after the treatment was terminated (with an average of thirty-three minutes).

*Foot.*—The effect upon the foot was comparable to that observed in the forearm. A significant augmentation in the rate of blood flow was uniformly elicited by mecholyl iontophoresis, the average maximal increase being 2.4 times the control level. The augmented blood flow continued for from thirty to ninety minutes after the termination of the iontophoresis (with an average of fifty-eight minutes).

In an attempt to determine the optimal conditions for the blood flow response, the forearm was exposed to a period of ten and then twenty minutes of iontophoresis. Likewise, the effect of a current density of 5 to 7 milliamperes was compared with that observed with one of 12 to 15. No clear-cut evidence was obtained to indicate that the longer period of treatment elicited a greater vasodilator response than the one of shorter duration, and similarly that the higher current density was more efficacious than the lower one. In fact, in the case of each of the two sets of conditions, no significant and consistent difference was noted

either in the highest level of blood flow induced, in the total increase in flow, or in the duration of the augmented circulation in the period following the treatment.

In order to localize the site of action of the drug, the following was performed. The effect of mecholyl iontophoresis was first determined in the forearm at a bath temperature of 32° C., and, after the blood flow had returned to the initial control level, the temperature of the water in the plethysmograph was raised to 45° C. in order to produce maximal vasodilatation of cutaneous blood vessels; the muscle circulation was only slightly affected by such a procedure.<sup>7</sup> When the flow had reached a constant maximal level, mecholyl iontophoresis was again begun. The response in Fig. 1 is typical. It demonstrates that, when the cutaneous vessels are fully dilated by heat, only a small increase in total blood flow is produced by mecholyl iontophoresis.

In order to determine whether or not the vessels in the muscles were capable of being vasodilated under these conditions, the forearm, still exposed to a bath temperature of 45° C., was subjected to a five-minute period of arterial occlusion. Immediately after the release of the pressure, blood flow measurements were obtained during the first minute of reactive hyperemia. In every instance the readings in this period were significantly greater than the previous resting blood flow. Since the skin vessels were already fully dilated by the heat, this increase in total flow during reactive hyperemia was necessarily due to vasodilatation of the blood vessels in the muscle.

In respect to systemic responses, none of any significance was noted in the subjects. At times there was a moderate increase in pulse rate and decrease in blood pressure. At the onset of the iontophoresis, a pins-and-needles feeling was generally experienced locally, but this disappeared within a few minutes. In one subject, 1 c.c. of prostigmin methylsulfate, 1:2,000, was injected subcutaneously about fifteen minutes before iontophoresis was begun, according to the suggestion of Loman and his associates.<sup>8</sup> In this instance, as contrasted with all of the above cases, alarming cardiovascular symptoms appeared. The subject became pale and complained of marked palpitation and a light-headed feeling; the pulse rate increased very significantly; and the blood pressure decreased.\* Although this procedure produced a slightly greater increase in peripheral blood flow as compared with that obtained with mecholyl iontophoresis alone, it was felt that the untoward reactions resulting therefrom mitigated the value of the effect obtained. For this reason, the use of prostigmin in conjunction with mecholyl iontophoresis was considered to have no practical importance, and hence no further studies along this line were attempted.

\*The explanation for such results probably rests on the fact that ordinarily with mecholyl iontophoresis a certain quantity of the drug penetrates the skin but is readily destroyed by choline esterase. However, if prostigmin is injected previously so as to inhibit the esterase, then the mecholyl enters the blood stream in sufficient concentration to elicit systemic effects.

## DISCUSSION

The use of meeholyl iontophoresis to increase the peripheral circulation appears to be justified by the results obtained in the present investigation on the forearm and foot and by the previous studies of Montgomery and his associates on the hand.<sup>4</sup> However, the findings in the leg would tend to indicate that the procedure does not have as much value if used for the purpose of augmenting blood flow in this region. Of interest in this respect is the observation that nicotinic acid also increases the circulation to the forearm and hand, but has little effect upon the blood vessels in the leg.<sup>9</sup>

The fact that only a slight increase in blood flow was found to occur when the skin vessels were first fully dilated, as by the application of local heat, strongly suggests that under ordinary environmental conditions the effect of meeholyl by iontophoresis is primarily upon cutaneous circulation and that the drug does not penetrate significantly into the muscle layers. The findings that iontophoresis with methylene blue affects only the superficial structures and that the deeper fascia and muscle are unstained even after an application of one hour's duration<sup>10</sup> would be in accord with this view.

On the basis of these observations it is possible to explain, in part at least, the uniformly good results with meeholyl iontophoresis in those states in which the skin circulation is altered, such as Raynaud's syndrome and other vasospastic conditions,<sup>10, 2</sup> indolent, nonhealing varicose and trophic ulcers,<sup>2, 3a</sup> and scleroderma.<sup>11</sup> Similarly, the reason for the negative, indefinite and equivocal data in the case of diseases of the muscle blood vessels<sup>10, 2</sup> is also clear, since this procedure does not appear to affect these vessels. Of course, it is possible that this difference may also be related to the occlusive character of the pathologic processes involving the deeper blood vessels.

It is of interest to note that the highest blood flow readings resulting from meeholyl iontophoresis at 32° C. were not as great as those produced merely by raising the temperature of the water in the plethysmograph to 45° C. (Fig. 1). This would imply that meeholyl iontophoresis, in the dosage used, does not produce a maximal vasodilatation of the skin vessels and that it is not as potent an agent in this respect as is heat. It is important to bear in mind, however, that the application of heat to an extremity with diminished blood supply is not without the danger of producing a severe burn. On the other hand, if moderate care is taken in the application of the electrodes, this objection does not hold in the case of meeholyl iontophoresis.

## SUMMARY

1. The vasodilating action of meeholyl by iontophoresis was studied in the forearm, leg, and foot of nine normal subjects by means of the venous occlusion plethysmographic method.

2. It was found that this procedure immediately produced a significant increase in the rate of blood flow in the forearm and foot, which continued for some time after the treatment was terminated. The effect upon the leg was less marked.

3. The increase in flow was considered to be primarily the result of vasodilatation of cutaneous blood vessels, those in the muscles probably contributing little if at all to the effect.

The authors wish to express their appreciation to Mrs. William Littleford and Mr. John Prince for valuable technical assistance.

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## MIXED INFECTIONS IN BACTERIAL ENDOCARDITIS

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THE primary etiologic agent of endocarditis is regarded very generally as a single species of bacteria growing upon the valvular endocardium, and very little emphasis has been laid upon the occurrence of mixed infections with unrelated organisms. Instances of mixed infections in bacterial endocarditis have been reported by Horder,<sup>1</sup> Howell et al.,<sup>2, 3</sup> Blumer,<sup>4</sup> Libman,<sup>5</sup> Thayer,<sup>6</sup> Davis and Weiss,<sup>7</sup> Segal,<sup>8</sup> and Middleton and Burke.<sup>9</sup> Thayer<sup>6</sup> and Davis and Weiss<sup>7</sup> each mentioned one instance in which three distinct organisms were obtained from a single patient. Repeated blood cultures during life positive for two organisms are recorded by Howell et al.,<sup>2, 3</sup> and in another instance<sup>2</sup> a single heart valve vegetation at post-mortem examination yielded two different organisms. Very little comment regarding mixed infections is made, except by Libman<sup>5</sup> and Thayer,<sup>6</sup> who apparently considered such cases as primary bacterial endocarditis of one type with "secondary" or "terminal" infections by other organisms.

Instances of transient "secondary" bacteremias or of "terminal" infections with positive post-mortem cultures of the heart's blood, but not valvular vegetations, have been presented by Wright,<sup>10</sup> DeSanto and White,<sup>11</sup> Martin and Adams,<sup>12</sup> Shiling,<sup>13</sup> Doane,<sup>14</sup> and Khairat,<sup>15</sup> but apparently these authors did not regard such cases as examples of bacterial endocarditis due to several organisms.

It is noteworthy that a review of several series of cases analyzed by Clawson,<sup>16</sup> Kreidler,<sup>17</sup> Horder,<sup>18, 19</sup> Sprague,<sup>20</sup> Fulton and Levine,<sup>21</sup> Musser,<sup>22</sup> Brink and Smith,<sup>23</sup> Capps,<sup>24</sup> Bayles and Lewis,<sup>25</sup> and Christian,<sup>26</sup> in addition to the recent textbooks by White<sup>27</sup> and Levine,<sup>28</sup> failed to disclose any reports of, or comment regarding, mixed infections in bacterial endocarditis.

In view of the fact that we have had the opportunity of observing six patients with bacterial endocarditis, whose blood repeatedly yielded two or more distinct species of bacteria, we feel it sufficiently worthwhile to present brief abstracts of these cases, together with a discussion of the clinical and bacteriologic problems involved.

From July, 1930, to July, 1941, at Duke Hospital, seventy-seven instances of bacterial endocarditis have been observed. In the years 1930

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to 1938, thirty-nine patients with this disease were seen and only one patient (Case 1) had multiple organisms. From 1938 to 1941, in the course of an intensive study of bacterial endocarditis, twenty-eight classical cases were observed clinically and bacteriologically. The blood of five of these patients was repeatedly positive for two or more organisms. In view of the above and the fact that no case diagnosed clinically as bacterial endocarditis has failed to yield positive blood cultures during this period of study, we feel the technique of our method merits a brief review.

In all instances of suspected bacterial endocarditis, blood for culture is taken daily at the height of the fever for four to seven consecutive days. Fifteen to 20 c.c. of blood are obtained by venipuncture from the patient and introduced into a flask containing 4 c.c. of sterile 2.5 per cent sodium citrate solution. The agar in five media tubes (one containing 15 c.c. of 0.1 per cent glucose beef infusion agar, pH 7.4, one containing 15 c.c. of North's gelatine agar, and three tubes containing 15 c.c. of plain beef infusion agar pH 7.4) is melted before the blood is obtained from the patient, and to each of the tubes of molten agar, cooled to 40° C., 2 c.c. of the patient's citrated blood are added, and after being mixed thoroughly, are poured into Petri dishes (one dish for each tube of agar). North's gelatine blood agar (for gonococci) is poured into the top of a Spray dish<sup>29</sup> and incubated in the presence of 10 per cent carbon dioxide. The remaining citrated blood is added to a flask containing 100 c.c. of beef infusion broth, pH 7.4. All of the cultures are incubated at 37° C. The plates are kept for five days, and the flask of broth, for two weeks, before they are reported to be negative. All cultures are examined daily. After the first forty-eight hours' incubation, if no colonies are visible on the plates, 5 c.c. of the supernatant broth are transferred from the flask to a sterile centrifuge tube. After centrifugalization at high speed for fifteen minutes, the supernatant fluid is discarded, a loopful of the sediment is streaked over the surface of each of two blood agar plates and on a slide for a stained smear. One plate is incubated under anaerobic conditions. This procedure is repeated at three-day intervals, until there is sufficient growth for identification. If colonies are present in the poured plates, smears are made of each type of colony (if more than one type is present) and stained by Gram's method. Transplants of the colonies are made to suitable media.

In most instances the organisms, isolated from the present group of patients, grew in the poured plates of the routine cultures of the blood. Because gonococcal endocarditis was suspected in Case 3, three cultures were planted in North's gelatine agar and in ascitic fluid dextrose broth, pH 7.4. A Gram's stain of the broth revealed gram-positive cocci in chains and gram-negative diplococci. Transplants were made to three North's gelatine blood agar plates, one of which was incubated aerobically, and one anaerobically; the third was incubated in the presence

of 10 per cent carbon dioxide. The streptococcus grew only in the anaerobic culture, and the gram-negative diplococcus grew only on the plate incubated in the presence of 10 per cent carbon dioxide. The organism was identified as *Neisseria gonorrhoeae*. Subsequent cultures were incubated both anaerobically and in the presence of 10 per cent carbon dioxide.

A Gram's stain of the hemolytic colonies in the poured plates of the blood of Case 2 revealed pleomorphic gram-negative rods suggestive of the Hemophilus group of organisms. Transplants were made to broth containing the "X" and "V" growth promoting factors. This organism was identified as *Hemophilus para-influenzae*.<sup>30</sup>

The aerobic streptococci were classified according to Brown's<sup>31</sup> and to Sherman's<sup>32</sup> criteria.

#### REPORT OF CASES

**CASE 1. History.**—P. T., a 52-year-old white business executive and engineer, was admitted to Duke Hospital on Sept. 10, 1932, complaining of fever of one month's duration. His past history revealed typhoid fever and frequent malarial chills as a young man, frequent colds prior to an antrum operation at 37, and mild prostatic symptoms for two years. His present illness began on Aug. 14, 1932, one month before entry, when he developed rather suddenly severe headache, malaise, and fever without chills. His fever continued at a level of 99° F. to 102° F., and pains in his legs and arms appeared. He entered the hospital for diagnosis, because of persistent fever, fatigue, and malaise.

**Physical Examination.**—The temperature was 38° C.; the pulse rate was 68; and respirations were 20. Examination revealed a well-developed, slightly undernourished white man of 52 in no obvious discomfort. His skin and mucous membranes were clear; no petechiae were observed. The eyes, ears, nose, mouth, and throat showed only enlarged tonsils and a dark left maxillary antrum on transillumination. The neck revealed no abnormalities. The lungs were perfectly clear. The heart was normal in size, shape, and rhythm. No definite murmurs were audible. The peripheral vessels were soft. The abdomen was normal, except for a well-healed appendectomy scar. The spleen was not felt. The genitals were normal. The prostate was diffusely enlarged. The prostatic secretion yielded many white blood cells. The finger tips and toes were very painful to pressure. Neurologic examination was negative.

**Laboratory Data.**—The hemoglobin was 76 per cent; the red blood cell count, 3,750,000; and the white blood cell count, 9,500, with 79 per cent polymorphonuclear leucocytes. The blood Wassermann reaction was negative. Urinalysis showed only a few white blood cells. Nasal cultures were positive for *Staphylococcus aureus* and prostatic cultures for *Staphylococcus albus*. Roentgenograms of his teeth showed no abscesses. The left antrum and ethmoids were cloudy, interpreted by the roentgenologist as old thickened membrane. Teleroentgenogram revealed normal lungs and heart. Initial cultures of the blood revealed *Streptococcus hemolyticus*; later cultures yielded both *Streptococcus hemolyticus* and *Streptococcus viridans*.

**Course in the Hospital.**—The patient was placed at bed rest and was given a normal diet and multiple blood transfusions. The first four cultures of the blood, taken between September 13 and 21, yielded only *Streptococcus hemolyticus* (three to ten colonies per cubic centimeter), but on September 22, a blood culture grew out four colonies each of *Streptococcus hemolyticus* and *Streptococcus viridans*, and three subsequent cultures were positive for both organisms (one to ten colonies per cubic centimeter of the former, and four to ten colonies per cubic centimeter of the

latter). The patient stayed in the hospital eighty-eight days, and in spite of blood transfusions, antistreptococcic serum, and sodium cacodylate, his course was steadily and progressively downhill. His fever was persistently elevated, generally between 38° C. to 39° C., rising to 40° C. to 41° C. with chills. Gradually he developed multiple emboli, a palpable spleen, clubbed fingers, systolic and diastolic mitral murmurs, an aortic diastolic murmur, a typical Corrigan pulse, and severe anemia. He was discharged on Dec. 7, 1932, to return home, where his course was rapidly downhill. Death occurred on Jan. 14, 1933, five months after the onset of his disease. No autopsy was obtained.

*Final Diagnosis.*—Bacterial endocarditis due to *Streptococcus hemolyticus* and *Streptococcus viridans* involving the mitral and aortic valves.

*Summary.*—This case was very interesting because of the age of the patient, older than average, the fairly sudden onset of his disease, and the absence of a demonstrable heart lesion at entry. The painful fingers and toes, suggesting peripheral emboli, were the outstanding physical findings pointing to endocarditis. The fact that the first four blood cultures taken during the fifth week of his disease were positive for *Streptococcus hemolyticus* might indicate this organism as the "primary" etiologic agent, with "secondary" invasion of the vegetation by *Streptococcus viridans*, which appeared in four subsequent cultures along with the former organisms. No clinical features were present to indicate a mixed infection. *Streptococcus viridans* infection could not be called a "terminal" infection, since it appeared during the seventh week of the disease. The course of the infection was typical of endocarditis, but not specifically of any distinctive type, being longer than acute endocarditis due to a pyogenic organism, and slightly shorter than the usual case of subacute (*Streptococcus viridans*) endocarditis.

**CASE 2. History.**—Miss F. C., a 21-year-old single, unemployed, white woman entered the hospital on June 25, 1938, complaining of weakness of three months' duration. The past history was of interest in that at the age of 12 she had had classical rheumatic fever involving multiple joints for three months. During the intervening nine years she had had little difficulty, save for transient joint pain five years before entry, and slight to moderate diminution in cardiac reserve. Her present illness began in February, 1938, five months before admission, when she developed a febrile illness, with unproductive cough and night sweats. Her convalescence was rapid and uneventful, but in March, 1939, she relapsed, with increasing weakness, general malaise, low-grade fever, and left upper quadrant pain along with tenderness in the finger tips. She was forced to bed three months before entry, because of weakness and weight loss of undetermined amount, and hospitalization was advised because of one blood culture positive for *Streptococcus viridans*.

*Physical Examination.*—The temperature was 38° C.; the pulse rate was 120; and respirations were 22. Examination revealed a fairly well-developed, but undernourished, chronically ill young white girl, bright and cooperative, in no real distress. Her skin was dry, pale, and delicate. Petechiae were present in the right conjunctiva, the left forearm, and beneath the nail of the left little finger. The eyes, ears, nose, mouth, and throat exhibited a tiny flame-shaped hemorrhage in the left optic fundus and enlarged tonsils. The neck was normal. The lungs were clear. The heart was enlarged to the left; the apex was localized in the fifth intercostal space 10.5 cm. from the midsternal line. By percussion there was prominence of the left upper arc. A marked systolic thrust and a late diastolic thrill were palpable over the precordium. At the apex the first sound was accentuated, and systolic and mid and late diastolic murmurs were audible. Faint systolic and early diastolic murmurs were heard over the aortic area. The rhythm was normal. The blood pressure was 112/54. The pulse was soft and Corrigan in type. The abdomen was relaxed; the right kidney was easily felt, and the spleen was palpated 3 fingerbreadths below the

left costal margin. Pelvic and rectal examinations were not abnormal. The extremities revealed clubbing of the fingers. The reflexes were physiologic.

*Laboratory Data.*—The hemoglobin was 51.6 per cent; the red blood cell count, 2,940,000; and the white blood cell count, 5,250, with 63 per cent polymorphonuclear leucocytes. The sedimentation rate was 32 mm. per hour, corrected. While the admission urine was entirely negative, later analyses showed a few red blood cells and positive benzidine reactions. Blood nonprotein nitrogen was 25 mg. per cent. Stool examination was essentially negative. Teleroentgenogram showed moderate cardiac enlargement. An electrocardiogram was normal, except for slurring of the QRS complexes in Lead I. Blood cultures were positive for *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic). Agglutinins were present initially in the blood serum in dilutions of 1:40 for the former and 1:20 for the latter organism. These titers rose later to 1:80 and 1:160, respectively.

*Course in the Hospital.*—The patient was placed at bed rest and was given a soft diet with supplementary vitamins, iron, liver, and repeated blood transfusions. During the first two weeks in the hospital her temperature fluctuated daily from 37° C. to 39.8° C. Fresh crops of petechiae developed, and she had one chill, the temperature rising to 40° C. Seven consecutive cultures of the blood were positive for *Streptococcus viridans* (one to eighteen colonies per cubic centimeter) and *Hemophilus para-influenzae* (hemolytic) (one to twenty-six colonies per cubic centimeter). On July 1, she was given 25 c.c. of anti-influenzal serum intravenously, followed by an anaphylactic reaction, which responded satisfactorily to adrenalin, coramine, and oxygen. Five days later she was given 340 c.c. of the same serum intramuscularly without reaction. On July 7, serum sickness developed, and on the same day 88 c.c. of 1 per cent aqueous solution of methylene blue were administered intravenously, followed by a generalized burning sensation, sweating, and blueness of the skin, lasting several days. She was discharged against advice on July 9, twenty-four days after admission, unimproved. Five blood cultures (a total of twelve) meanwhile were consistently positive for *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic). A specimen of blood for culture, sent to us after her discharge on July 21, was still positive for both organisms. Death occurred while the patient was at home on Sept. 2, 1938, about seven weeks after discharge. No autopsy was obtained.

*Final Diagnosis.*—Rheumatic carditis, inactive, with cardiac enlargement, mitral stenosis and insufficiency, and aortic insufficiency. Bacterial endocarditis due to *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic) superimposed on aortic and probably mitral valves.

*Summary.*—Of interest in this case were the presence of pre-existing inactive rheumatic heart disease with mitral and aortic valve lesions, the onset of her disease with fever and symptoms from the respiratory tract, indicating the probable portal of entry of the organisms, and the blood cultures (a total of 13), repeatedly positive for both *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic). There were no features by history, physical examination, or clinical course to suggest a "primary" organism, or even to suggest the presence of a mixed infection, yet the repeatedly positive blood cultures, uninfluenced by therapy leave little doubt that both organisms were present in the heart valve vegetations and were etiologically important.

*CASE 3.\* History.*—Mrs. S. C., a 24-year-old white housewife, was admitted to Duke Hospital on Sept. 25, 1938, complaining of fever with chills for about three months. Three months before entry during a normal pregnancy, she developed very suddenly chills, high fever, and multiple painful swollen joints, which later subsided, except for continued swelling of the left knee. Paracentesis of the joint yielded

\*This case was reported in detail previously by the authors, New England J. Med. 221: 167, 1939.

purulent fluid but no organisms. A blood culture was negative at this period, but a gonococcal complement fixation test was 4+. Spontaneous delivery of a normal child was followed by a brief remission of her symptoms. However, she soon relapsed with irregular recurring chills, high fever, marked sweating, gradual weight loss, and partial ankylosis of the knee. An adequate course of sulfanilamide and three blood transfusions were administered without therapeutic effect, prior to hospitalization here.

*Physical Examination.*—The temperature was 39.8° C.; the pulse rate was 116; and the respirations were 24. Examination revealed a pallid, slender, poorly developed, undernourished white woman of 24, who appeared acutely ill. The skin was pale, but warm and there were no petechiae nor emboli. The spine and lymphatic systems were not remarkable. The eyes, ears, nose, mouth, and throat were normal, except for hypertrophied, infected tonsils. The cervical veins were not distended. The lungs presented a few fine crepitant râles after cough at the angle of the right scapula. The heart's apex was in the fifth intercostal space 9 cm. from the midsternal line, indicating slight but definite cardiac enlargement. At the apex a faint protodiastolic gallop rhythm was present. Over the pulmonary area, a soft systolic murmur and a high-pitched, early, pulmonary diastolic murmur, transmitted to the third interspace, were heard, and  $P_2$  was accentuated. The rhythm was regular. The peripheral arterial walls were soft. The blood pressure was 100/70. The abdomen was normal; the spleen was not felt. Pelvic examination revealed erosive cervicitis. The left knee showed partial ankylosis. No clubbing of the fingers or of the toes was evident.

*Laboratory Data.*—The hemoglobin was 60 per cent; the red blood cell count, 3,050,000; and the white blood cell count, 10,500, with 78 per cent polymorphonuclear neutrophils. Repeated urinalyses revealed a few white blood cells. Sedimentation rate was 37 mm. per hour, corrected. Blood Wassermann test was negative. Gonococcal complement fixation test was 4+ on two occasions. An electrocardiogram was normal. Teleroentgenogram revealed an infarct in the right lung, and a globular heart with slight enlargement. Cervical smears and cultures were negative for *Neisseria gonorrhoeae*. Repeated blood cultures were positive for *Neisseria gonorrhoeae* and a non-hemolytic anaerobic streptococcus.

*Course in the Hospital.*—The patient was placed at strict bed rest and given a high-vitamin diet, iron, liver, and repeated blood transfusions. During the first five hospital days, daily chills with fever rising to 38.7° C. to 40.4° C. were evident, and five consecutive blood cultures, taken daily at the height of fever, were positive for *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus, the colony counts being less than one colony per cubic centimeter of blood in each instance. Sulfapyridine was administered orally in gradually increasing doses from 1.2 to 5 Gm. per day for fifty-two days. The temperature fell abruptly to normal and rose to 39.5° C. on the twelfth day of therapy. A blood culture yielded the anaerobic streptococcus, but was negative for *Neisseria gonorrhoeae*. Eight days later, the temperature rose again to 38° C., but the blood culture was negative and three subsequent cultures, taken at weekly intervals thereafter, were all negative. She remained afebrile and asymptomatic throughout the remainder of her hospital stay, felt well, and gained in weight and strength. She was discharged well, on Nov. 27, 1938, sixty-three days after entry. Opsonins, agglutinins, and bactericidins, initially absent or in low titer, appeared and increased to high titer for both organisms at the time of discharge. The gonococcal complement fixation test, initially 4+, became negative. Re-examinations at intervals of approximately one and four months after discharge revealed the patient well, the pulmonary murmur persisting, and blood cultures entirely negative. The patient was last heard from by letter in January, 1940, and reported her health as excellent.

*Final Diagnosis.*—Bacterial endocarditis due to *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus involving the pulmonary valve.

*Summary.*—A classical example of bacterial endocarditis involving the pulmonary valve is presented. The fact that five consecutive cultures of the blood were positive for two organisms, *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus, suggests that both organisms were probably present in the bacterial vegetations on the pulmonary valve. The clinical history was quite typical of gonococcal endocarditis, and there were no features, except for the positive blood cultures to suggest the presence of a mixed infection. It should be noted that under sulfapyridine therapy the gonococcus disappeared from the blood stream prior to the anaerobic streptococcus. While this indicates greater sensitivity of the gonococcus to the drug, it may indicate also that the streptococcus organisms were deep in the vegetations rather than superficially located, and certainly demonstrates the necessity of drug therapy, adequate to eradicate both organisms, before cure of the patient can be effected.

*CASE 4. History.*—H. E., a 21-year-old, unoccupied, white woman was admitted to Duke Hospital on Jan. 5, 1939, complaining of pain in the left upper quadrant of her abdomen for three days. Her past history revealed that she had had a "leaking heart" since early childhood, but there was no history of rheumatic fever, chorea, scarlet fever, or tonsillitis. Her present illness began one month before admission, when she developed malaise, weakness, and fever without chills. She was hospitalized elsewhere for two weeks, and a diagnosis of rheumatic fever was made. Three days prior to admission here she developed sudden severe sharp pain beneath the left costal margin aggravated by inspiration and cough. Her fever had been relatively constant, and weight loss of indeterminate amount had been noted.

*Physical Examination.*—The temperature was 39° C.; the pulse rate was 90; and respirations were 20. Examination revealed a well-developed but slender, swarthy, attractive girl of 21, complaining of pain in the left flank. The skin was hot and dry. No petechiae were noted. The mucous membranes were pale. The eyes, ears, nose, mouth, and throat were not remarkable, except for enlarged tonsils, and a reddened pharynx. The neck veins were prominent, and the thyroid was symmetrically enlarged. The lungs were clear. The heart was enlarged slightly to the left, the apex being in the fifth intercostal space 8.5 cm. from the midsternal line. At the apex there was a systolic thrill, a harsh blowing systolic murmur and a late diastolic murmur. The rhythm was normal. The pulse was soft. The blood pressure was 110/70. The abdomen showed exquisite tenderness in the left upper quadrant where the spleen was just palpable and tender. A friction rub was heard over the splenic area. Pelvic and rectal examinations were normal. The extremities were not remarkable. The reflexes were normal.

*Laboratory Data.*—The hemoglobin was 60 per cent; the red blood cell count, 2,900,000; and the white blood cell count, 9,520, with 86 per cent polymorphonuclear leucocytes. The sedimentation rate was 36 mm. per hour, corrected. Repeated urinalyses showed only one to three white blood cells per high-power field in uncatheterized specimens. The blood Wassermann and Kahn reactions were negative. Stool examination was negative. Fluoroscopy of the chest and teleroentgenogram showed obliteration of the left costophrenic angle by a small amount of fluid, and generalized cardiac enlargement, with rapid weak pulsations. A flat plate of the abdomen was negative. Two electrocardiograms were abnormal due to slurred QRS complexes in Lead I, and inversion of T<sub>1</sub> and T<sub>2</sub>, and diphasic T<sub>3</sub>. Blood cultures were positive for *Streptococcus fecalis* and *Streptococcus hemolyticus*. Initial studies of immune antibodies revealed negligible phagocytosis and negative agglutinations. Subsequent studies showed slight phagocytosis, and agglutination titers to both organisms in serum dilutions of 1:1280.

*Course in the Hospital.*—She was placed at bed rest and given a high-calorie, high-vitamin diet, supplemented with liver and iron. A total of eleven blood transfusions was given during her hospital stay. During the first week in the hospital her temperature was persistently elevated with swings from 37.4° C. to 39.8° C., and five consecutive blood cultures were positive for *Streptococcus fecalis* (four to thirteen colonies per cubic centimeter) and *Streptococcus hemolyticus* (seven to twenty-six colonies per cubic centimeter). On January 9, she was started on sulfapyridine, 4 to 5 Gm. daily for a period of twenty-three days, during which time her temperature dropped very slightly. Six of seven cultures of the blood taken during this interval were negative for *Streptococcus hemolyticus*, but all were positive for *Streptococcus fecalis*. Therapy was then shifted to neoprontosil intramuscularly and orally for a period of ten days. A high fever returned, and three cultures were positive for both organisms during prontosil therapy. On February 12 (thirty-eighth hospital day), the patient was given sodium sulfanilyl sulfanilamide in doses of 3 Gm. daily for one week without effect. On February 15, for a period of four days the patient was given 200 c.c. of polyvalent antistreptococcal serum, without benefit, and on February 26, 200 c.c. of anti-enterococcal serum were given, without reaction. Subsequently sulfapyridine and sodium sulfapyridine were given orally in large doses (9 Gm. per day) without benefit. She continued febrile, with repeated emboli, and sixteen blood cultures (a total of thirty-one) were positive for *Streptococcus fecalis* and *Streptococcus hemolyticus*. On March 5, because of severe right lower quadrant pain, an appendectomy was performed, and a normal appendix was removed, and only numerous petechiae were found in the intestinal wall. Her white blood cell count and sedimentation rate remained elevated during her entire period of hospitalization. In view of failure of improvement, the patient was discharged on April 4, 1939. No follow-up notes are available, with regard to her further course.

*Final Diagnosis.*—Rheumatic carditis, inactive, with slight cardiac enlargement, mitral stenosis and insufficiency. Bacterial endocarditis due to *Streptococcus fecalis* and *Streptococcus hemolyticus* superimposed on the mitral valve.

*Summary.*—The patient presented rheumatic heart disease with mitral stenosis and insufficiency with the onset of bacterial endocarditis, one month prior to entry. There was no indication by history of the portal of entry, nor of the specific organism responsible for the disease. The disclosure of five consecutive blood cultures, positive for *Streptococcus fecalis* and *Streptococcus hemolyticus* in significant numbers, early in the disease one month after onset, in the absence of any other focus of infection suggests that both organisms were etiologically responsible for the bacterial endocarditis. The therapeutic import of this fact is revealed by the disappearance of the *Streptococcus hemolyticus*, but not the *Streptococcus fecalis* under sulfapyridine therapy, and the later blood cultures positive for both organisms. It is to be noted that the re-exhibition of sulfapyridine did not affect the *Streptococcus hemolyticus*, which meanwhile had become "sulfapyridine fast." It would seem that both organisms must be removed if endocarditis is to be cured, since temporary sterilization of but one organism is generally followed by the reappearance of that organism at a later date when therapy is discontinued.

*CASE 5. History.*—Mrs. O. C., a 45-year-old white housewife, was admitted to Duke Hospital on Dec. 31, 1939, complaining of fever of eight months' duration. Her past history revealed the presence of a "heart murmur" with mild dyspnea on exertion for twenty-seven years and scattered, poorly localized, transient muscle and joint pains, for four years. Her present illness began insidiously eight months before admission with the gradual onset of malaise, weakness, anorexia, intermittent fever without chills, and generalized muscle pains, most marked in the cervical region. Progressive weight loss and general decline in health followed. Several abscessed teeth were removed three months before entry with striking exacerbation of her

symptoms, and emboli were noted to fingers, toes, and spleen. A course of sulfanilamide was given without benefit. By the time of admission to the hospital she had lost 25 pounds in weight.

*Physical Examination.*—The temperature was 39.5° C.; the pulse rate was 100; and the respirations were 22. Examination revealed a well-developed, poorly nourished, almost emaciated white woman of 45, who appeared chronically ill, complaining of pain in the left lower chest. The skin, spine, and lymphatics showed nothing remarkable, except for a fatty tumor of the left thigh, and several small, bruised areas on both legs. Petechiae were evident in the right conjunctiva. The eyes, ears, nose, mouth, and throat revealed only dental repair and extractions, and pallor of the mucous membranes. The neck exhibited muscle stiffness and pain on motion. The cervical veins were not distended. The lungs contained transient râles at the left base where a faint friction rub was audible. The heart was enlarged to the left, the apex being in the fifth intercostal space 10.5 cm. from the mid-sternal line; prominence of the left upper arc by percussion was noted. A loud harsh systolic murmur and a late rumbling diastolic murmur were audible over the apex.  $P_2$  was accentuated and greater than  $A_2$ . No basal murmurs were heard. The rhythm was regular. The blood pressure was 140/90. The peripheral vessels were normal. Abdominal examination revealed the liver and spleen to be palpable just below the costal margins. There was a well-healed midline scar, and tenderness in both upper quadrants. The pelvic and rectal examinations were normal. The fingers and toes were quite tender, with early clubbing. The reflexes were physiologic.

*Laboratory Data.*—The hemoglobin was 85 per cent; the red blood cell count, 4,370,000; the white blood cell count, 12,750, with 87 per cent polymorphonuclear neutrophils. The sedimentation rate was 36 mm. per hour, corrected. Urinalysis showed a trace of albumin, one or two white blood cells, one or two red blood cells, and an occasional hyaline cast per high-power field. Stool examination was negative. Blood Wassermann and Kahn reactions were negative. Teleroentgenogram revealed the lungs to be clear. The heart was greatly enlarged to the left, and the left auricle was dilated. The electrocardiogram was abnormal, due to slurred QRS complexes, ventricular premature beats, and inverted  $T_2$ . Repeated blood cultures were positive for *Streptococcus viridans* and *Streptococcus hemolyticus*.

*Course in the Hospital.*—The patient was placed at bed rest and was given a high-vitamin diet, with supplementary vitamins, iron, liver, and repeated blood transfusions. During the first week in the hospital, her temperature was persistently elevated with peaks from 38° C. to 39° C., and six consecutive cultures of the blood were positive for *Streptococcus viridans* (two to thirty-eight colonies per cubic centimeter), and *Streptococcus hemolyticus* (one to thirty-four colonies per cubic centimeter). On the eighth and ninth hospital days, single test doses of 4 Gm. of sodium sulfapyridine were administered intravenously. A blood culture was still positive for *Streptococcus viridans* (four colonies per cubic centimeter) and *Streptococcus hemolyticus* (less than one colony per cubic centimeter). On the tenth and eleventh days, 6 and 12 Gm. of sodium sulfapyridine were given intravenously, the blood concentrations rising to 19.8 mg. per cent and 24 mg. per cent, respectively. A blood culture taken twelve hours later was sterile, and eighteen subsequent cultures taken bi-weekly until the patient's discharges were all negative, except for one obviously contaminated blood culture. The temperature dropped to normal after the fourth intravenous drug injection and except for occasional rises to 37.9° C. remained normal during the patient's entire hospital stay. Oral administration of the drug in doses of 10 Gm. per day at four-hour intervals was then substituted, the blood concentrations averaging 9.9 mg. per cent. She tolerated the drug poorly and gradual fall in weight of 6 kg. was noted. Under continued drug therapy, progressive anemia, in spite of repeated transfusions, was manifested. The white blood cell count fell to normal by the twenty-fifth day, but the sedimentation rate remained



very active. With the disappearance of the bacteremia, immune antibodies for both organisms appeared in the patient's blood in moderately high titer by the time of discharge. The patient left the hospital against advice on Feb. 24, 1940, the fifty-fifth hospital day, after forty-eight days of continuous therapy. She was discharged on sulfapyridine, 5 Gm. daily. Her physician reported gradual decline in health, with fever, toxemia, cardiac dilatation, cardiac failure, and death in May, 1940, three months after discharge. No autopsy was obtained. A specimen of blood for culture sent to us on April 23, 1940, was positive for *Streptococcus viridans* (six colonies per cubic centimeter) and *Streptococcus hemolyticus* (less than one colony per cubic centimeter). Tests for immune bodies in the blood serum revealed a marked reduction in titers of agglutinins and bactericidins.

*Final Diagnosis.*—Rheumatic carditis, inactive, with cardiac enlargement, mitral stenosis, and insufficiency. Bacterial endocarditis due to *Streptococcus viridans* and *Streptococcus hemolyticus* superimposed upon the mitral valve.

*Summary.*—This patient exhibited the common clinical background of bacterial endocarditis (i.e., rheumatic heart disease with mitral stenosis and insufficiency) and her history and subsequent course were quite typical of *Streptococcus viridans* endocarditis. There were no features to suggest a *Streptococcus hemolyticus* infection, nor a mixed infection, but the presence of six consecutive cultures of the blood, prior to therapy, positive for both *Streptococcus viridans* and *Streptococcus hemolyticus* in significant numbers, very definitely suggests that both organisms were present in the heart valve vegetations. The disappearance of both organisms simultaneously under therapy and their reappearance after the discontinuance of therapy, in the absence of any other demonstrable focus, is evidence of the etiologic importance of both organisms.

*CASE 6. History.*—Mrs. A. S., a 51-year-old housewife, was admitted to Duke Hospital on Jan. 14, 1941, complaining of weakness of three months' duration. Her present illness began in October, 1940, three months prior to admission, when she developed fever and chills, and shortly thereafter, cough productive of small amounts of blood, dyspnea, and increasing weakness. Anorexia, nausea, vomiting and hematuria followed. One month after onset she was hospitalized by her own physician, because of weakness, high fever, and recurrent chills. A brief remission in chills followed two blood transfusions. She was referred to this hospital because of persistent fever, chills, weakness, and weight loss of 40 pounds within three months.

*Physical Examination.*—The temperature was 36.8° C.; the pulse rate was 100; and respirations were 18. Examination revealed a pallid, emaciated white woman of 51, who was acutely ill. The skin and mucous membranes were pale, and petechiae were scattered over the trunk and limbs and in the right conjunctiva. Examination of the eyes, ears, nose, mouth, and throat revealed pyorrhea of the gums and marginal atrophy of the tongue. The neck veins were engorged. The lungs showed numerous moist râles bilaterally, which were greater on the right, with dullness and diminished breath sounds at the right base. The heart was moderately enlarged with the apex in the fifth intercostal space at the anterior axillary line. A soft, blowing systolic murmur was audible at the apex, but no diastolic murmur was heard. The rhythm was regular. The blood pressure was 120/68. The liver was enlarged to the umbilicus, firm, but tender, and the spleen was felt 3 fingerbreadths below the left costal margin. The pelvic examination was normal, except for relaxation of the pelvic floor and retroversion of the uterus. There was no clubbing of the fingers or of the toes. Neurologic examination was negative.

*Laboratory Data.*—The hemoglobin was 49 per cent; the red blood cell count, 2,670,000; and the white blood cell count, 7,200, with 86 per cent polymorphonuclear leucocytes. A sedimentation rate, corrected was 14 mm. per hour. Blood Wassermann and Kahn reactions were negative. Repeated urinalyses showed albumin, vary-

ing numbers of red blood cells, a few white blood cells, and granular casts per high-power field. Stool examination was negative. Electrocardiogram showed sinoauricular tachycardia, low voltage, and slurred QRS complexes and flat T waves in all leads. Teleroentgenogram revealed cardiac enlargement and a triangular area of density at the right base obscuring the right costophrenic angle. Stool and urine cultures grew only *Escherichia coli*. Blood cultures yielded *Streptococcus viridans* and *Streptococcus hemolyticus* growing in symbiosis with an unidentified gram-negative rod.

*Course in the Hospital.*—The patient remained in the hospital twenty-eight days, during which time her temperature was persistently elevated with daily peaks in temperature from 37.8° C. to 39.8° C. She was given a high-vitamin diet, supplemented with iron, liver, and blood transfusions, and was completely digitalized. During the first five hospital days, four consecutive cultures of the blood were positive for *Streptococcus viridans* (three to ten colonies per cubic centimeter of blood) and *Streptococcus hemolyticus* growing in symbiosis with an unidentified gram-negative rod (100 to 228 colonies per cubic centimeter of blood). Sulfadiazine was given orally about 4 Gm. per day for six days, beginning January 21, and 1 to 2 Gm. daily for four days thereafter. On January 22 the sulfadiazine concentration in the blood was 8.8 mg. per cent, and the blood nonprotein nitrogen was 66 mg. per cent. Three consecutive blood cultures taken during sulfadiazine concentrations of 9.2 to 14.2 mg. per cent were positive only for *Streptococcus viridans* (four to ten colonies per cubic centimeter). Sulfadiazine was discontinued on January 30, because the blood nonprotein nitrogen rose to 108 mg. per cent. Meanwhile the patient became weaker, the heart murmur louder, and congestive failure deeper in spite of therapy. Two subsequent blood cultures (on January 27 and on February 10) showed *Streptococcus viridans* (thirty-eight to forty colonies per cubic centimeter) and the mixed organisms noted above (two to 148 colonies per cubic centimeter). On February 7 she developed agranulocytosis, with a white blood cell count of 700; three days later all polymorphonuclear leucocytes had disappeared from the peripheral blood, and the bone marrow was almost entirely devoid of myeloid cells. She went downhill rapidly; coma ensued, with a blood nonprotein nitrogen of 135 mg. per cent; edema progressed. The patient died quietly on Feb. 12, 1941.

Autopsy revealed a typical vegetative endocarditis, with huge greenish vegetations involving the tricuspid valve, and smaller vegetations on the aortic valve, and old rheumatic scarring of the mitral valve and chordae tendinae. Multiple infarcts were present in both lungs, and a large pulmonary embolus involved the superior branch of the right pulmonary artery. Emboli were present in an acute splenic tumor and in both kidneys. Microscopic sections of the vegetations of the heart valves showed the classical findings of bacterial endocarditis with cocci deep in the base of the valvular vegetations. Cultures of the heart's blood and the vegetations from the tricuspid and aortic valves revealed *Streptococcus viridans*, *Streptococcus hemolyticus*, and the unidentified gram-negative rod.

*Final Diagnosis.*—Bacterial endocarditis due to *Streptococcus viridans*, *Streptococcus hemolyticus*, and an unidentified gram-negative rod, involving the tricuspid and aortic valves. Rheumatic carditis, inactive, with old mitral valvulitis.

*Summary.*—This patient provided data of exceptional interest from the clinical, bacteriologic, and pathologic standpoints. Her history and subsequent course were typical of bacterial endocarditis, complicated by cardiac failure and renal insufficiency. The development of agranulocytosis following sulfadiazine therapy undoubtedly precipitated premature death, although the pathologists felt that pulmonary embolism from the tricuspid valve vegetations was the actual cause of exodus. The finding of three organisms (*Streptococcus viridans*, *Streptococcus hemolyticus*, and an unidentified gram-negative rod) in the first 4 consecutive blood cultures was very unusual, although here again there was nothing to suggest the presence of a

mixed infection. The persistence of *Streptococcus viridans* in the blood cultures during therapy suggested only the relative resistance of this species of bacteria to chemotherapy. Of paramount importance in the problem of etiology was the post-mortem bacteriologic demonstration of all three organisms in the heart's blood culture and in cultures taken from both aortic and tricuspid valves.

#### DISCUSSION

The clinical features of six cases of classical bacterial endocarditis, in which blood cultures were repeatedly positive for two or more organisms, have been presented. In five instances two organisms were consistently present, while in the sixth, three organisms were isolated. In two instances (Cases 1 and 5) the organisms were *Streptococcus viridans* and *Streptococcus hemolyticus*, while in the others the organisms were *Streptococcus viridans* and *Streptococcus hemolyticus* growing in symbiosis with an unidentified gram-negative rod (Case 6), *Streptococcus viridans* and *Hemophilus para-influenzae* (hemolytic) (Case 2), *Streptococcus fecalis* and *Streptococcus hemolyticus* (Case 4), and *Neisseria gonorrhoeae* and a nonhemolytic anaerobic streptococcus (Case 3). In the first five instances noted above, the organisms were grown on routine laboratory media, while in the sixth the possibility of *Neisseria gonorrhoeae* was suspected, and appropriate media were employed.

A careful analysis of the history, physical findings, routine laboratory data, and clinical course of these patients reveals little that may be considered distinctive of mixed infections. The necessity for careful bacteriologic studies as the only means of identifying the presence of mixed infections is thus emphasized.

The recognition of such mixed infections in bacterial endocarditis is of fundamental importance in the therapy of the disease, since all organisms must be eradicated from the blood and the heart valve vegetations if cure of the patient is to be accomplished. This is clearly illustrated by Case 3, where both organisms (*Neisseria gonorrhoeae* and anaerobic streptococcus) proved sensitive to a single drug, resulting in recovery, and in Cases 4 and 6, where the *Streptococcus fecalis* and the *Streptococcus viridans* proved resistant to sulfonamide therapy, while the hemolytic streptococci, sensitive in both patients, disappeared from the blood stream temporarily, and later returned after the discontinuance of therapy. Indeed, from the brief experiences reported here, a single organism could not alone be eradicated permanently, for, in each instance after the discontinuance of therapy, the organism, thus temporarily eliminated, returned in cultures before death.

In instances of mixed infections, it seems very certain that both organisms are present not only in the blood but in the vegetations as well. The finding of consecutive blood cultures repeatedly positive for several organisms strongly favors this view, when there is no obvious focus present, other than the heart valve vegetation, to shed organisms into

the blood stream. The demonstration of mixed organisms in the valvular vegetations at autopsy (Case 6) is proof of this assumption. Blood cultures repeatedly positive for the same organisms eliminate the possibility of simple contamination.

When the blood of patients suffering from bacterial endocarditis yields two or more organisms, the question of the specific etiologic relationship of each organism to the disease is an interesting and important one. In the pathogenesis of such cases undoubtedly the valve is first invaded by one organism, and later the vegetations of the first are invaded by the second organism. The determination of which organisms are "primary" and which are "secondary" is extremely difficult in the majority of instances, and in but two of our cases (Case 1 and Case 3) were we reasonably certain that the hemolytic streptococcus and the gonococcus were the "primary" organisms. We do not feel that additional or "secondary" organisms are "terminal" infections, since they have appeared too early in the course of the disease process and particularly since opsonins, agglutinins, and bacterioidins, when present, were in about equal titer for both organisms. Regardless of the terminology used in mixed infections, when two or more organisms are present in the vegetations on the heart valves, each must be considered of etiologic significance, because all must be eradicated before cure of the patient can be effected.

#### CONCLUSIONS

1. Six cases of classical bacterial endocarditis have been presented, in which two or more organisms were cultured repeatedly from the patients' blood.
2. The clinical, bacteriologic, and pathologic aspects of the problem have been discussed.
3. The importance of the bacteriologic demonstration of the presence of mixed infections in bacterial endocarditis is emphasized, because of the etiologic relationship of such organisms to the disease and the therapeutic problem involved.

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# A COMPARISON OF ELECTROCARDIOGRAPHIC CHANGES OBSERVED DURING THE "ANOXEMIA TEST" ON NORMAL PERSONS AND ON PATIENTS WITH CORONARY SCLEROSIS

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**A**LTERATIONS in the form of the electrocardiogram caused by induced anoxemia have been used to estimate the functional efficiency of the coronary circulation. Evidence has been presented indicating that the "anoxemia test" affords an index of the coronary reserve. An apparatus and a technique for performing the test have been described, and criteria for an abnormal response have been proposed.<sup>1-3</sup> If properly done, the procedure is simple and safe. Various unpleasant reactions which may be encountered have been reported.<sup>3</sup> Gilbert and his associates have employed the method in a study of the effects of various drugs upon patients with "angina of effort,"<sup>4, 5</sup> and they have expressed the opinion that "the experiment is perfectly humane and without danger."<sup>4</sup>

In the light of further experience, it seemed desirable to analyze critically the results of tests on normal persons and on patients with coronary sclerosis, with particular reference to differences in the electrocardiographic changes observed in the two groups.

## MATERIAL AND METHOD

The analysis is based upon the results of 293 tests, of which 136 were done on persons who were regarded as normal, in the sense that they were free of cardiac disease, and 157, on patients with coronary sclerosis. The criteria for the diagnosis of coronary sclerosis were a history of anginal pain, cardiac enlargement, as shown in the teleroentgenogram, and an abnormal electrocardiogram. The presence of any two of these was considered sufficient. Cases in which there were other possible etiologic factors were not included. The normal group comprised twenty women and 116 men, ranging in age from 21 to 73 years. Of the normal subjects, twenty-eight were over 50 years old, and, of these, four were over 70. The group with coronary sclerosis included 136 patients with a history of anginal pain and forty-three who were known to have healed cardiac infarcts; their ages ranged from 35 to 77 years.

In a number of these cases only one test was performed. When more than one was done, the first was selected whenever possible. No test was included during which there occurred any unusual or unpleasant reaction, such as one of those noted in an earlier paper.<sup>3</sup>

The procedure previously described was employed.<sup>2, 3</sup> The subjects breathed a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes unless

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cardiac pain was experienced before the end of that time. Four-lead electrocardiograms were taken routinely just before the test was started and at intervals of five minutes thereafter. If the patient complained of discomfort, a record was quickly taken, the low-oxygen mixture was shut off, and 100 per cent oxygen was administered for one minute. The precordial lead used was the one commonly designated as IVF. All electrocardiograms were measured by at least two observers. When the RS-T deviation was measured, the level of the P-R interval was taken as the isoelectric line, and readings were made to the nearest half millimeter. In each test the result was based on the difference between the control and the record showing the maximal changes during induced anoxemia. As will be pointed out, it was not invariably the last electrocardiogram in which the greatest alterations were found.

### RESULTS

*Occurrence of Pain.*—Since none of the normal persons experienced pain, the test lasted the full twenty-minute period in every case. Of the 157 patients with coronary sclerosis, seventy-four (47 per cent) complained of pain, and, in fifty-four (63 per cent) of those who had pain, the discomfort appeared during the first ten minutes (Fig. 1). A positive test was observed in seventy-seven (49 per cent); pain occurred in 27 per cent and was absent in 22 per cent. The test was negative in eighty (51 per cent); pain occurred in 20 per cent and was absent in 31 per cent (Table I). It has previously been pointed out that the occurrence of pain, even in the absence of significant electrocardiographic changes, affords *presumptive* evidence of a diminished coronary reserve. Its appearance during the first ten minutes of a negative test is of particular importance. In a follow-up study of fourteen such cases, four patients later showed a positive test, one had an attack of coronary occlusion, and two died of their cardiac disease.<sup>3</sup> If, then, in this series of 157 cases of coronary sclerosis the positive reactions are added to negatives during which pain occurred, the test furnished evidence of coronary insufficiency, actual or presumed, in 109, or 69 per cent.

TABLE I

INCIDENCE OF PAIN IN 157 PATIENTS WITH CORONARY SCLEROSIS IN RELATION TO THE RESULT OF THE ANOXEMIA TEST

|           | POSITIVE |    | NEGATIVE |    |
|-----------|----------|----|----------|----|
|           | NO.      | %  | NO.      | %  |
| With pain | 42       | 27 | 32       | 20 |
| No pain   | 35       | 22 | 48       | 31 |
| Total     | 77       | 49 | 80       | 51 |

*Deviation of the RS-T Segments.*—No normal person showed a total RS-T deviation greater than 2.5 mm., and in only seven was this figure reached (Fig. 2A). In the individual leads, a deviation of 1.5 mm. was observed in one case; a deviation of 1 mm. occurred in twenty-five leads in twenty-one cases. In contrast to the normal group, sixty-two patients with coronary sclerosis developed a total RS-T deviation of

3 mm. or more; in nine of these the change measured more than 5 mm. (Fig. 2B). In the individual leads, deviations varied from zero to 5 mm., and a change of 1 mm. or more occurred in 185 leads in ninety-two cases. The average RS-T deviation for each lead in patients with coronary sclerosis was greater than that for the corresponding lead in the normal subjects. The difference was most marked in Leads I and IVF (Fig. 3).

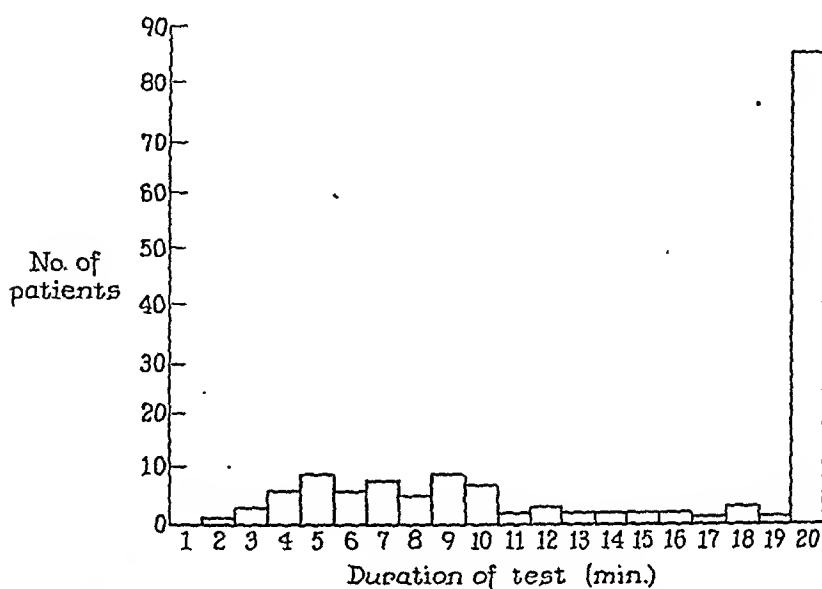


Fig. 1.—Duration of the anoxemia test in 157 cases of coronary sclerosis. Tests shorter than twenty minutes were terminated at the onset of pain.

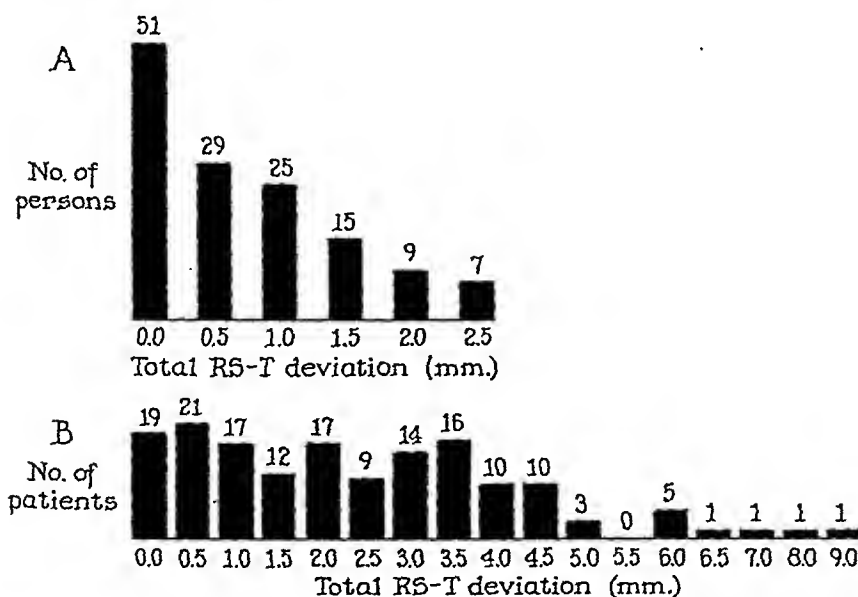


Fig. 2.—Total RS-T deviation which occurred during the anoxemia test. A, in 136 normal persons; B, in 157 patients with coronary sclerosis.

In many of the cases of coronary sclerosis the total deviation increased in linear fashion as the test progressed (Figs. 4 and 5). In



some, the degree of deviation rose to a peak and then decreased (Fig. 6). The latter sequence of events suggested that compensatory mechanisms in the circulation had brought about a favorable adjustment in coronary blood flow.<sup>6</sup> One of the methods of adaptation appeared to be an increase in pulmonary ventilation.<sup>7</sup> Several patients have given

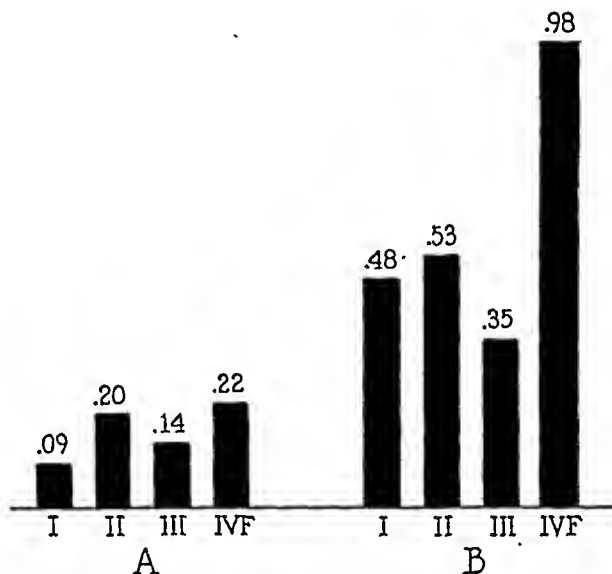


Fig. 3.—Average RS-T deviation which occurred in each lead during the anoxemia test. A, in the normal group; B, in the patients with coronary sclerosis.

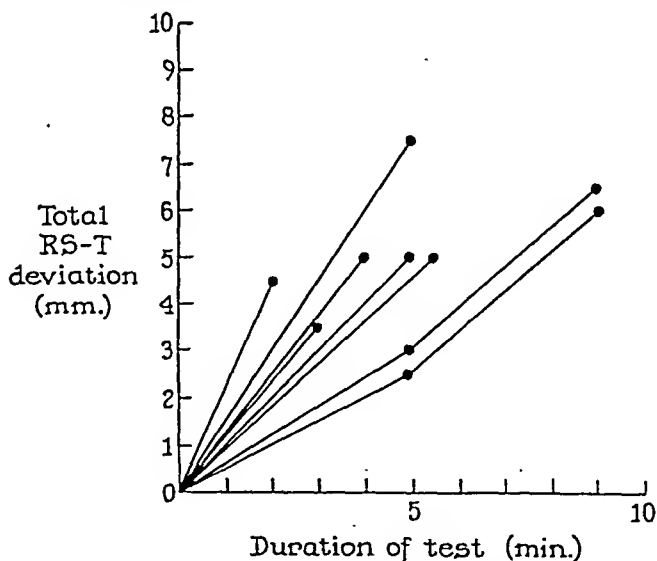


Fig. 4.—Marked RS-T deviation in eight tests on a patient with coronary sclerosis. Pain appeared during the first ten minutes. This man later died suddenly.

an account of their pain which makes it seem likely that similar adjustments take place on effort. One man stated that he had discomfort on beginning to walk, but that this wore off after he had "limbered up." He could then continue for an indefinite time, provided he did not hurry. A similar experience on the golf course was described by

another patient. While playing the first hole or two he was likely to have pain; thereafter, he could go on without being aware of his heart.

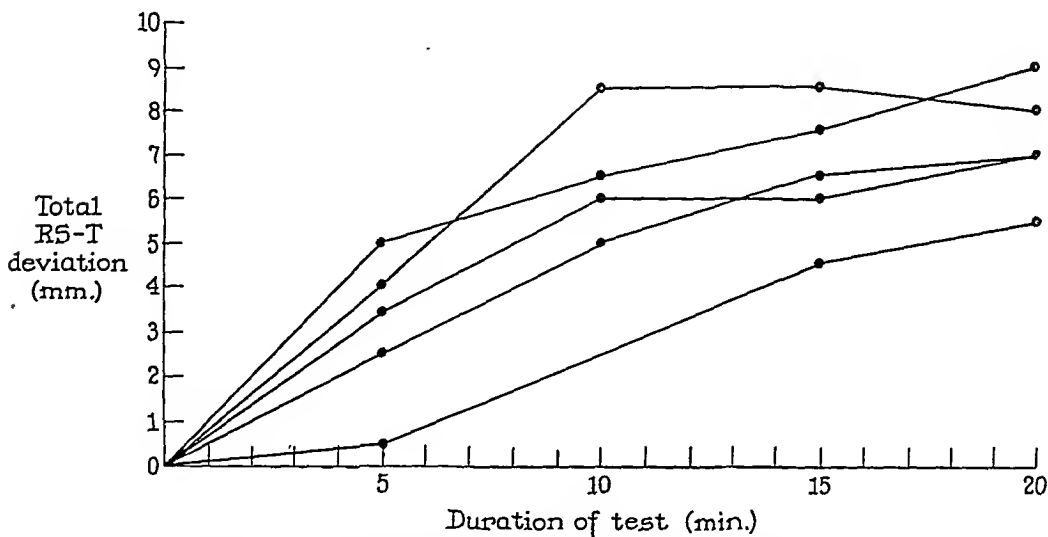


Fig. 5.—Marked RS-T deviation in five tests on a patient who never experienced pain during anoxemia. He later had an attack of coronary occlusion with cardiac infarction.

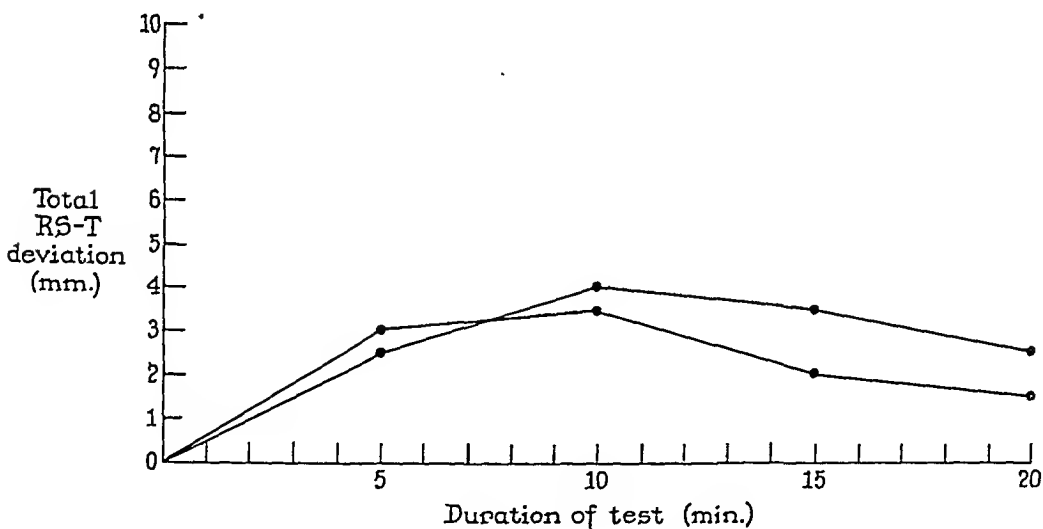


Fig. 6.—RS-T deviation in two patients with coronary sclerosis who did not experience pain during the test. There was apparent compensatory adjustment of the coronary circulation, as shown by the initial rise in the curve, followed by a fall.

In comparing the results on different patients with coronary sclerosis, no direct relationship could be demonstrated between the degree of RS-T deviation and the duration of the tests; patients who breathed the low-oxygen mixture for twenty minutes did not tend to show greater RS-T changes than those whose tests were terminated at the end of five or ten minutes because pain was felt (Fig. 7). In other words, the duration of the test did not determine the absolute magnitude of total RS-T deviation.

Age likewise did not affect the degree of RS-T deviation, either in normal subjects or in patients with coronary sclerosis.

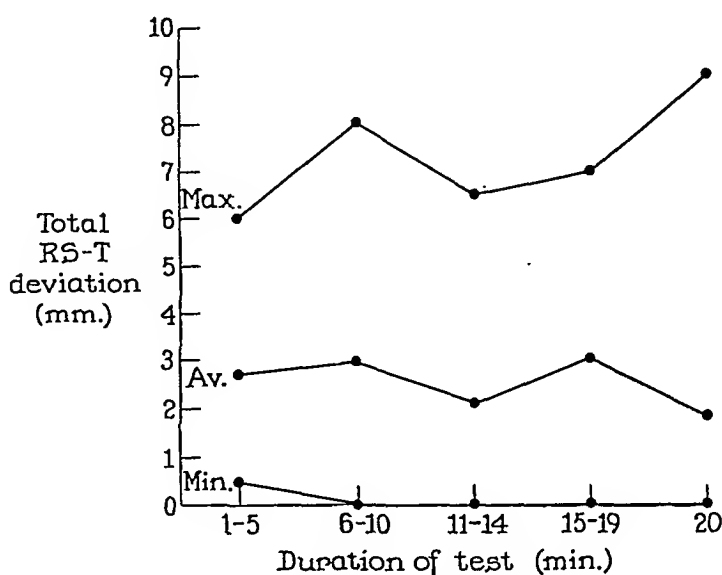


Fig. 7.—The maximum, average, and minimum total RS-T deviations in relation to the duration of the test in the group with coronary sclerosis.

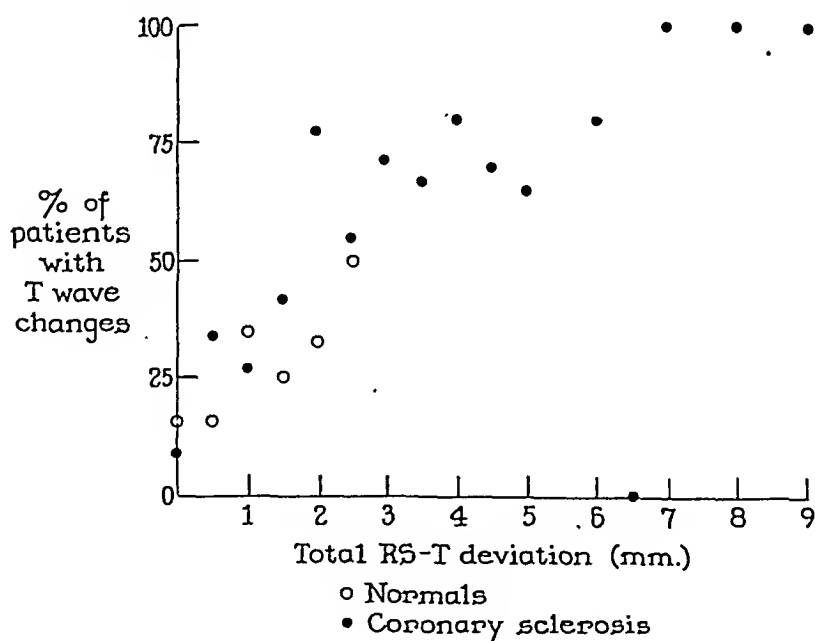


Fig. 8.—Percentage of normal and coronary patients who showed T-wave changes, in relation to the degree of RS-T deviation.

*T-Wave Changes Alone.*—By change in the T wave, partial or complete reversal in its direction is meant, whether this be from upright to inverted or the opposite. In both groups the incidence of such a change increased with the degree of total RS-T deviation (Fig. 8). There was one exception, in which a deviation of 6.5 mm. was unaccompanied by any change in the T waves. A comparison of the occurrence of T-wave changes in normal subjects and in patients with coronary sclerosis showed an almost equal percentage in Lead III, but, in

Leads I, II, and IVF, reversal of T was more often observed in the coronary group. The difference was most striking in Leads I and IVF (Fig. 9). In not a single normal person was the direction of T in IVF completely reversed, whereas in the coronary patients this was noted in twenty-three tests. Furthermore, in the coronary group, T-wave changes occurred in more than one lead in forty-five tests (28.6 per cent), whereas in the normal patients multiple changes were observed only five times (3.7 per cent).

Age did not affect the incidence of RS-T changes, either in normal patients or in the patients with coronary sclerosis.

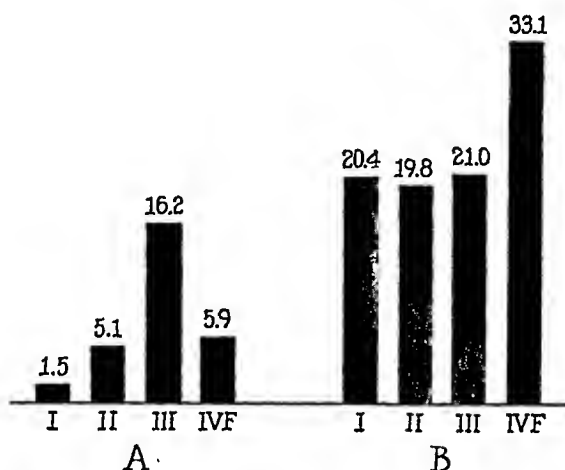


Fig. 9.—Percentage of subjects who showed partial or complete reversal in the direction of the T wave during the test. The figures for each lead are given separately. A, normal patients; B, coronary patients.

*T-Wave Changes Associated With RS-T Deviations.*—In the normal patients a change in the direction of the T wave never occurred in association with an RS-T deviation of 1 mm. or more. In the coronary group, on the other hand, this was observed in twenty-one cases. T in IVF was partially reversed, with an associated RS-T deviation of 1 mm. or more, in two normal subjects and in seventeen cases of coronary sclerosis. T<sub>2</sub> was partially or completely reversed, with an associated RS-T deviation of 1 mm. or more, in two tests on normal subjects and in sixteen patients in the coronary group. The same combined changes were noted with respect to T<sub>3</sub> twice in normal persons and ten times in coronary patients.

#### DISCUSSION

The usefulness of the anoxemia test depends primarily upon the validity of the criteria which distinguish a normal from an abnormal reaction. On the basis of previous experience, four types of change in the four-lead electrocardiogram which occur as the result of induced oxygen want have been described as indicative of a diminished coronary reserve.<sup>2, 3</sup> Examination of the results on the 136 normal subjects included in this study showed that, in two (1.4 per cent), there ap-

peared electrocardiographic changes which were heretofore regarded as evidence of coronary insufficiency. Both of these subjects were in the third decade of life. The changes observed were referred to as "criterion 4" in earlier papers, and consisted of partial reversal in the direction of the T wave in Lead IVF, accompanied by an RS-T deviation of 1 mm. or more in this lead. In the group of 157 coronary cases, the test was positive in seventy-seven (49 per cent), but in only three cases (1.8 per cent) was the test considered positive solely on the basis of this criterion. In all of the remaining cases, other criteria of a positive reaction were also present. It is thus apparent that the combination of partial T-wave reversal and an RS-T deviation of 1 mm. or more in the precordial lead occurs in a small number of persons with normal hearts; and that, as an isolated observation, it is rarely helpful in the recognition of coronary insufficiency. In this series of cases, it was noted with about equal frequency in normal subjects and in patients with coronary sclerosis. Accordingly, the use of criterion 4 has been discontinued. It is our present opinion that the test is positive when *any one* of the following is found:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm. or more.

2. There is partial or complete reversal of the direction of the T wave in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

3. There is complete reversal of the direction of the T wave in Lead IVF, regardless of any associated RS-T deviation in this lead.

Strong presumptive evidence of diminution in the coronary reserve is afforded by the occurrence of pain during a test which is electrocardiographically negative. The successful use of pain as an index will depend upon the observer's ability to differentiate it from the minor discomfort of an apprehensive subject, and his astuteness in detecting the occasional malingerer. A complaint of pain should not be considered presumptive evidence of a positive test when payment for disability insurance is involved.

#### SUMMARY

1. In 157 cases of coronary sclerosis, the anoxemia test was electrocardiographically positive in 49 per cent, and furnished presumptive evidence of coronary insufficiency, by the occurrence of pain, in another 20 per cent. It was thus helpful in the recognition of a diminished coronary reserve in 69 per cent.

2. The RS-T deviation in each individual lead, as well as the total RS-T deviation in the four leads which were employed, was greater in the 157 patients with coronary sclerosis than in 136 normal persons.

3. The amount of total RS-T deviation usually increased in linear fashion in relation to the duration of the period of anoxemia. Occa-

sionally the degree of deviation rose to a peak level and then decreased, suggesting that compensatory mechanisms operated to bring about a favorable adjustment in coronary blood flow.

4. Comparison of the results on different patients with coronary sclerosis showed no direct relationship between the duration of the test and the amount of total RS-T deviation; patients who breathed the low-oxygen mixture for twenty minutes did not tend to show greater RS-T deviation than those whose tests were terminated earlier because of pain.

5. The incidence of significant T-wave change increased with the degree of total RS-T deviation.

6. The combination of partial T-wave reversal and RS-T deviation of 1 mm. or more in Lead IVF, as the sole criterion of a positive test, was observed in less than 2 per cent of the cases of coronary sclerosis and was found with equal frequency in normal persons. Its use as a sign of a positive reaction has, therefore, been discontinued.

#### ADDENDUM

Since this paper was prepared for publication there has appeared an article by C. T. Burnett, M. G. Nims, and C. J. Josephson (The Induced Anoxemia Test: A Study by Age Groups, *AM. HEART J.* **23**: 306, 1942), in which the authors have expressed certain conclusions that are at variance with our experience. A number of the questions raised by their observations have been answered by the incisive comments of Dr. Douglas Deeds, of Denver, published in the same issue of the *AMERICAN HEART JOURNAL* (p. 334). A reply to others will be found in a recent paper and in the discussion which followed its presentation (Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: The Anoxemia Test as an Index of the Coronary Reserve: Serial Observations on One Hundred and Thirty-Seven Patients With Their Application to the Detection and Clinical Course of Coronary Insufficiency, *J. A. M. A.* **117**: 2113, 1941). Some of the reasons for disagreement are here briefly recapitulated.

1. The studies of Burnett and his associates were carried out in Denver at an altitude of 5,420 feet, where the average barometric pressure is 630 mm. of mercury; at sea level this pressure averages 760 mm. of mercury. Thus, a 10 per cent oxygen mixture in New York is approximately equivalent to an 8 per cent concentration of oxygen when transferred to one mile above sea level. In addition, in at least six cases, through an error, Burnett used a mixture containing 8.6 per cent of oxygen.

2. Breathing a 10 per cent oxygen mixture at sea level simulates atmospheric conditions at an altitude of approximately 18,000 feet. If the test is done at an elevation of 5,420 feet, the altitude equivalent during induced anoxemia is about 23,420 feet. The strain imposed on the circulation by the altitude is disproportionately greater as more

rarefied atmospheres are attained, so that the change from 18,000 to 23,000 feet represents a greater increment of increase than does the transition from 13,000 to 18,000 feet.

3. It is an assumption, unsupported by evidence, that persons in Denver, "acclimatized" to the altitude by long residence, react to induced anoxemia as do those who live and are tested at sea level.

4. In not a single person with a normal cardiovascular system have we observed pain during a test. Some of Burnett's subjects experienced pain; and in 19.2 per cent of clinically normal persons he found an abnormal response, according to our criteria. But his so-called "normal" subjects were evidently not very carefully chosen. For example, a 47-year-old man (Case 39) experienced discomfort both during the test and for some time afterward. He also showed an abnormal response according to all criteria. This result is qualified by the ingenuous statement that "we learned later that he had some hypertension, without other evidence of cardiovascular abnormality."

5. According to Burnett, a negative response "may further cloud the clinical picture." We have repeatedly stressed the point that only a positive test is significant. A negative Wassermann reaction does not exclude the presence of syphilis. The value of any test depends upon its intelligent interpretation.

In summary, the observations of Burnett and his collaborators, because of the conditions under which they were made, are not comparable to those reported by us. Their conclusions, therefore, cannot be regarded as applying to the results of the "anoxemia test" which we have described.

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# THE RATIONALE OF OPERATIVE TREATMENT OF SUBACUTE BACTERIAL ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS

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CIRCULATORY failure and subacute bacterial endarteritis, usually of the *Streptococcus viridans* variety, constitute the two most important complications of patent ductus arteriosus. Although Munro,<sup>18</sup> in 1907, apparently was the first to suggest that circulatory disturbance might be corrected by ligation of the ductus, it was not until 1939 that Gross and Hubbard<sup>13</sup> reported the first such successful procedure and thereby demonstrated the effectiveness of surgical therapy in correcting circulatory abnormality.

The first attempt at operative treatment of subacute *Streptococcus viridans* endarteritis superimposed on patent ductus arteriosus, was reported by Graybiel, Strieder and Boyer<sup>11</sup> in 1938. (This, incidentally, represented the first effort ever made to operate upon a patent ductus arteriosus.) At operation, the right branch of the pulmonary artery was so intimately adherent to the ductus that an attempt to separate the two structures from one another appeared extremely hazardous. Accordingly, an effort was made to obliterate the lumen of the ductus by introducing a series of external plicating sutures. Unfortunately the patient succumbed on the fourth postoperative day, of acute gastric dilatation. At autopsy, the ductus was found to have been only partially occluded. Vegetations were present in the pulmonary artery and at the pulmonic orifice of the ductus. The lungs contained many small scattered infarcts, a few of which had undergone central softening and necrosis.

After noting the post-mortem findings outlined above, Graybiel, Strieder, and Boyer concluded that cure could not have been achieved in their case by the procedure which had been attempted. In support of their contention, they pointed out that, even if ductal occlusion had been accomplished successfully, it would not have destroyed the vegetations which existed within the ductus, let alone those within the pulmonary artery. They stated that the only procedure which *might* prove successful in such a case, was one that would remove *all* vegetations from direct contact with the blood stream: and they indicated

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that such an operation would have to consist of obliteration not only of the ductus but also of the adjacent portions of the pulmonary artery. Subsequently, Gross<sup>12</sup> warned against operation in the presence of superimposed infection, and stated, "Subacute bacterial endocarditis must be regarded as a contraindication to operation because the friable vegetations around the ductal opening will almost certainly be dislodged and result in embolism or a more severe bacteremia."

Following the unsuccessful effort reported by Graybiel, Strieder, and Boyer, no attempt at operative treatment of subacute bacterial endarteritis superimposed on patent ductus arteriosus was recorded until 1940.\* In June of that year, however, the author and Vesell presented four such cases before the annual meeting of The American Association for Thoracic Surgery.<sup>27</sup> The first patient recovered without benefit of chemotherapy and has remained entirely well up to the present time (more than two years since operation).<sup>26</sup> The second patient was unimproved (apparently because vegetations already were present upon the aortic valve) and died of the original subacute *Streptococcus viridans* infection about eight months later. The third and fourth patients succumbed of accidental hemorrhage during operation. In all four cases, the ductus was sclerotic, friable, and adherent to the pulmonary artery as in cases described by Abbott,<sup>1</sup> Graybiel, Strieder, and Boyer,<sup>11</sup> Hamilton and Abbott,<sup>14</sup> and Schlaepfer.<sup>20</sup>

In the following year, in an effort to reduce the difficulties and dangers of operation, the operative technique was modified;<sup>22</sup> and since then four additional patients suffering from relatively early infection, have been subjected to surgical treatment.† In these cases, operation consisted merely of division or ligation of the ductus without any attempt to perform the radical procedure which Graybiel, Strieder, and Boyer assumed to be a requisite of cure when vegetations exist in the pulmonary artery. Nevertheless, all four patients recovered promptly without benefit of chemotherapy.<sup>24, 25, 28</sup> Under the circumstances, it might be maintained that, since recovery ensued, vegetations were not present within the pulmonary artery. The investigations of Abbott<sup>1</sup> indicate, however, that in cases of infected patent ductus arteriosus, early involvement of the pulmonary artery is practically a constant finding. The latter was substantiated by the post-mortem findings, in the case reported by Graybiel, Strieder, and Boyer<sup>11</sup> and in two personal cases to which reference already has been made.<sup>27</sup> The duration of infection in these three cases varied between three and one-half and five months, and vegetations were found within the pulmonary artery in all.

\*In July, 1940, Keele and Tubbs,<sup>13</sup> of London, reported a case of infected patent ductus in which the patient survived operation but was not cured of infection. Following intensive chemotherapy, the blood cultures finally became sterile, thirteen months postoperatively.<sup>5</sup>

†Two patients suffering from infection of long duration also have undergone operation. Since they fall within a special group, now under investigation, they are excluded from the present discussion.

In the author's five successful cases, the duration of infection varied between one and four months, and, although the interior of the pulmonary artery could not be inspected at operation, it seems warranted to assume that vegetations already were present within the lumen. Even if it were conceded, for purposes of discussion, that vegetations were not present within the pulmonary artery, all will agree that vegetations were present within the ductus. It also will be agreed that such vegetations could not have been removed completely from contact with the circulating blood, by so simple an operation as ductal ligation or division. Inasmuch as the latter procedures were followed by recovery, without benefit of chemotherapy, some explanation of their efficacy must be offered.

The author's theory of the mechanism of recovery, rests partly upon observations which are supported by clinical and laboratory data and partly upon assumptions for which only indirect evidence is available at present. It therefore is offered not as the only possible explanation of cure, but rather as a tentative hypothesis which appears to be best supported by the evidence at hand. Under the circumstances, it is quite likely that, in the light of future investigation and observations, the following viewpoint may require some modification.

#### PATHOLOGIC ANATOMY AND PHYSIOLOGY

In those instances in which patent ductus arteriosus is unassociated with other congenital cardiovascular abnormalities, such as subaortic or pulmonic stenosis, coarctation of the aorta, and septal defects, evidence has been presented by Eppinger, Burwell and Gross<sup>9</sup> to indicate that the direction of the hemie flow through the ductus is essentially from the aorta toward the pulmonary artery. This is assumed to be due to the fact that, throughout the cardiac cycle, the pressure of blood in the aorta is higher than in the pulmonary artery. The current, which swirls through the ductus and impinges upon the wall of the pulmonary artery opposite the orifice of the ductus, eventually produces thickening of the intima and atheromatous plaque formation within the ductus and pulmonary artery. According to Buchwald<sup>6</sup> and to Rokitsansky,<sup>19</sup> such changes are most likely to be found at, or near, the pulmonic orifice of the ductus. When subacute bacterial infection supervenes, vegetations apparently develop chiefly upon these pre-existing sclerotic and atheromatous plaques.<sup>6</sup> *Thus, even early in the course of infection, vegetations usually are found not only in the ductus itself but in the pulmonary artery as well.* Abbott<sup>1</sup> has emphasized the frequency of early involvement of the pulmonary artery, by stating, "The pulmonary end of the ductus with the immediately adja-

\*Allen<sup>2</sup> has presented evidence to indicate that the development and growth of vegetations is favored in areas which are subjected to mechanical "impact and contact" by the infected blood stream. In cases of patent ductus arteriosus, the wall of the ductus and the wall of the pulmonary artery (opposite the orifice of the ductus) constitute such areas of impact and contact, and it is there that infected vegetations develop most commonly.

cent tissues (pulmonary artery) is always the initial seat of the vegetative inflammatory lesion."

The author assumes that, once vegetations have become established in the ductus and pulmonary artery, they are subjected to the unceasing trauma of the swirling ductal current. It is postulated that, as a result of the continuous agitation of the vegetations, infected emboli and organisms are broken off and enter the circulation more or less uninterruptedly. Organisms and infected emboli, derived from vegetations within the ductus and pulmonary artery, can enter the peripheral circulation only through two routes. The first is through the ductus directly into the aorta. The second is through the pulmonary circuit, to the left side of the heart, and then into the aorta.

Hubbard, Emerson, and Green,<sup>15</sup> in addition to Abbott,<sup>1</sup> have stressed the fact that vegetations within the ductus are situated most commonly at or near the pulmonic orifice of the latter structure. In view of the direction, velocity, and constancy of the hemic current which swirls through the ductus, it appears logical to assume that most of the infective material which is derived from vegetations within the ductus is swept into the pulmonary artery. On the other hand, it is known that reverse eddy currents often exist along the edges of a swiftly flowing stream, and it is quite possible that in cases of infected patent ductus a certain amount of infective material may be carried into the aorta by such currents. It is further assumed that septic emboli and organisms derived from vegetations within the pulmonary artery are swept almost exclusively into the branches of the pulmonary arterial tree, for, in order to enter the aorta directly, it would be necessary for such material to pass through the ductus against the full force of the continuously onrushing ductal current.

In certain cases vegetations, in addition to being present near the pulmonic orifice, may be found close to the aortic orifice of the ductus. This is especially true when the ductus is short. It is postulated that, in such cases, infective material may be carried into the aorta fairly freely, by the eddy currents to which reference already has been made. In rarer instances, the "ductus" consists merely of a fistulous opening between the aorta and the contiguous pulmonary artery. In such cases, it appears quite likely that infective material is shed directly into both the pulmonary artery and aorta.

From all of the foregoing theoretical considerations, it is assumed that, in the majority of cases of infected patent ductus arteriosus, the major portion of infective material derived from vegetations within the ductus and pulmonary artery is carried into the pulmonary circuit and only a relatively small amount enters the aorta directly through the ductus. In certain less common situations, however (*vide supra*), significant quantities of such material are assumed to enter the aorta as well as the pulmonary artery.

Evidence in favor of the entry of infected emboli and organisms chiefly into the pulmonary circuit is afforded by the following clinical and laboratory observations: (1) Episodes of spontaneous pulmonary embolization are quite common, even early in the course of infection; (2) during the early stages of infection, peripheral embolization is uncommon; (3) at post-mortem examination, vegetations are found within the pulmonary artery in almost every instance, and upon the pulmonic valve frequently; (4) at post-mortem examination also, even in cases in which infection has been of long duration, vegetations rarely are found within the aorta. The author recently demonstrated, by taking blood cultures simultaneously from the surgically exposed pulmonary artery and aorta of a patient suffering from patent ductus arteriosus with superimposed infection, that very many more organisms were present in the pulmonary artery than in the aorta.<sup>23</sup> In the absence of a feeding focus in the peripheral circulation or right side of the heart, the latter findings could be attributed only to the direct entry of organisms, into the pulmonary artery, from vegetative lesions situated within the ductus or pulmonary artery, or both.

An argument in favor of the assumption that a certain number of organisms enter the aorta directly through the open ductus is to be found in the author's observations concerning the amazing rapidity with which the peripheral blood cultures become negative following operation in certain cases.<sup>24-28</sup> (This subject will be discussed in detail in a forthcoming communication.) In certain rare instances, the entry of large amounts of infective material directly into the aorta is suggested at post-mortem examination, by the presence of vegetations within the aorta at some distance from the aortic orifice of the ductus. It also is indicated in the rare case in which peripheral embolization is noted during life, without vegetations being found in the left side of the heart or aorta at autopsy.

Animal experimentation<sup>3, 7, 8, 21, 29, 30</sup> and the author's observations,<sup>23</sup> in a patient suffering from *Streptococcus viridans* sepsis (vide supra), indicate that large numbers of organisms which enter the pulmonary circuit are removed in the lungs. However, the fact that peripheral blood cultures remain positive during the course of asepsis indicates that some organisms pass through the pulmonary capillaries to gain access to the general circulation. In this connection it seems logical to assume that a condition such as patent ductus arteriosus, in which the pulmonary artery and its radicles are dilated, may result in further impairment of the already inadequate pulmonary protective mechanism.

In patent ductus arteriosus, dilatation of the pulmonary arterial tree is due to an increase in the pressure, volume, and rate of flow of blood in the pulmonary artery, resulting from the arteriovenous shunt. (Such dilatation is recognizable in the roentgen film by an increase in size of the pulmonary artery and its larger branches and also by the presence

of bilateral pulmonary vascular congestion.) The author postulates that the combination of increased pressure, volume, and rate of flow of blood in the pulmonary artery also serves to create a powerful driving force which tends to facilitate the passage of organisms through the dilated vascular channels of the lung. As was stated previously, such organisms enter the pulmonary arterial blood from vegetative foci situated within the ductus and pulmonary artery.

#### THE EFFECTS OF OPERATION

Ligation or division of the ductus serves merely to *close the abnormal communication* which exists between the aorta and pulmonary artery. *No vegetations are removed from the ductus or pulmonary artery.* Nevertheless in five patients, of the six who survived operation, recovery ensued without benefit of chemotherapy. As the result of observations made in the successful cases, the author is of the opinion that *sterilization* of the peripheral blood stream *precedes recovery* rather than follows it. This statement is based upon the fact that the peripheral blood cultures become sterile so promptly that it is inconceivable that the residual vegetations within the ductus and pulmonary artery could have healed\* within so short a period of time (several minutes to several hours).

Surgical closure of a patent ductus arteriosus results in immediate restoration of the integrity of the aorta and pulmonary artery and in correction of the altered circulatory dynamics. As soon as the ductus is occluded, the forceful current which swirls from the aorta into the pulmonary artery is halted. The operation is assumed to produce three effects. (1) Vegetations within the ductus and pulmonary artery cease being violently traumatized. As a result, the dislodgment of infected emboli and organisms from these sources is greatly reduced. (2) Infective material, derived from vegetations situated on the pulmonic side of the ligature of the ductus, no longer can enter the aorta but must enter the pulmonary artery exclusively. (3) The pressure, volume, and rate of flow of blood in the pulmonary artery are restored to normal. This causes a disappearance of the powerful driving force, which formerly tended to facilitate the passage of infective material through the capillaries of the lung, and a prompt removal of the influences responsible for dilatation of the pulmonary artery and its branches (including presumably its finest radicles). Thus to summarize, it is postulated that closure of the arteriovenous shunt prevents the entry of organisms directly into the aorta, reduces the amount of infective material which is shed into the pulmonary circuit, and increases the efficiency of the pulmonary protective mechanism. As a result of the increase in efficiency of the pulmonary protective mechanism, relatively few organisms now are able to pass through the pulmonary capillaries to enter the peripheral circulation. Those which do enter apparently

\*A detailed report of the postoperative blood cultures in these cases will be presented in a separate communication.

are removed effectively by the protective mechanism of the general circulation (reticuloendothelial system); the blood cultures thus become sterile. (Cases in which vegetations are situated on the aortic side of the ligature of the ductus, upon the cardiac valves, and within the aorta, will not be discussed here. However it is assumed that, in general, they will not respond satisfactorily to operation.)

Before complete recovery takes place, the residual vegetations in the ductus and pulmonary artery must undergo healing. That the latter may and does occur is demonstrated conclusively by the disappearance of all clinical manifestations and laboratory evidence of infection within a short time of operation. Healing of vegetations is assumed to take place either as the result of alteration of local mechanical factors or changes in nutrition, or perhaps both. According to the mechanical theories cited by Allen,<sup>2</sup> *Streptococcus viridans* vegetations develop at points which are subjected to excessive mechanical impact and contact by the infected hemie current. (In patent ductus arteriosus, the abnormal stresses and strains are maximal in the ductus and in the pulmonary artery at a point opposite the orifice of the ductus, and vegetations usually are present at those sites.) According to Friedman, Katz, and Howell,<sup>10</sup> fibrin is precipitated from the blood stream and vegetations develop at points of local stress and strain. Viable organisms, as a rule, are found only in the superficial portions of vegetations. It is assumed that these organisms remain viable, because they are protected from the phagocytic action of the blood stream by fibrin which is being precipitated continuously upon the surface of the vegetations. In accordance with the theory of the above-mentioned authors, it is postulated that operation, by eliminating the swirling current in the ductus, results in diminished deposition of fibrin upon the surface of vegetations situated within the ductus and pulmonary artery. The organisms, being no longer protected, are destroyed by phagocytosis; the vegetations then undergo involution.

The theory that operative closure of the ductus alters the nutrition of the residual vegetations is favored by Libman,<sup>17</sup> and by Boldero and Bedford.<sup>4</sup> It is well known that in subacute *Streptococcus viridans* endocarditis complicating chronic valvular disease, vegetations are found much more commonly in the left side of the heart than in the right. The authorities cited above, believe that the higher oxygen content of blood in the left side of the heart may be an important factor in favoring the growth of vegetations there. In accordance with this theory, they have postulated that in cases of patent ductus arteriosus complicated by subacute *Streptococcus viridans* infection the growth and perpetuation of vegetations in the ductus and pulmonary artery may be favored by the abnormally high oxygen content of the blood in the latter structures as the result of the arteriovenous shunt. Thus, when the shunt is closed surgically, these vegetations now lacking an oxygen supply adequate for their continued growth, tend to undergo involution.

## SUMMARY AND CONCLUSIONS

Attention is called to the fact that involvement of the pulmonary artery by vegetations probably occurs at an early stage of infection concomitantly with the development of vegetations within the ductus itself.

It had been assumed previously by others that recovery could ensue in such cases only if operation were to consist of obliteration of the ductus and the involved adjacent portions of the pulmonary artery. Nevertheless, following simple division or ligation of the ductus, five of the author's patients recovered promptly without benefit of chemotherapy. Although the interior of the pulmonary artery could not be inspected at operation, it was assumed that vegetations were present.

The following explanation of recovery after the closure of infected patent ductus arteriosus, based upon certain assumptions and established facts, is offered tentatively. Vegetations develop within the ductus and pulmonary artery at the site of intimal thickenings and atheromatous plaques. The latter result from the trauma of the hemic current that swirls through the ductus and impinges upon the wall of the pulmonary artery opposite the orifice of the ductus. This current flows swiftly from the aorta toward the pulmonary artery, throughout the cardiac cycle, and continuously traumatizes the vegetations mentioned above. Infected emboli and organisms thereby are dislodged and, for the most part, are swept into the pulmonary circuit by the current in the ductus. Some organisms in all probability also enter the aorta through the ductus. In the presence of an open ductus, the pressure, volume, and rate of flow of blood in the pulmonary artery are increased. This results in dilatation of the pulmonary artery and all of its branches, including the finest capillaries, and also serves to create a powerful driving force which tends to facilitate the passage of organisms through the dilated pulmonary capillaries and into the peripheral circulation more freely than normally.

Ligation or division of the ductus serves merely to close the abnormal arteriovenous communication which exists between the aorta and pulmonary artery. At operation no vegetations are removed from the ductus or pulmonary artery.

The effectiveness of operation is explained as follows. As soon as the lumen of the ductus is obliterated, the swirling current in the ductus is halted abruptly, and its traumatizing action, upon vegetations within the ductus and pulmonary artery, ceases at once. As a result, the dislodgment of infective material into the circulation is greatly diminished. Infective material now can no longer enter the aorta through the ductus but must enter the pulmonary artery exclusively. At the same time, the factors responsible for dilatation of the pulmonary arterial tree are removed, and the driving force, which formerly tended to facilitate the passage of organisms through the dilated pulmonary

capillaries, disappears. This results in an increase in efficiency of the pulmonary protective mechanism. The relatively few organisms which pass through the pulmonary capillaries, to enter the peripheral circulation, now can be disposed of fairly readily by other protective forces of the body; the blood cultures usually become sterile within a short time.

Complete recovery occurs only after the residual vegetations within the ductus and pulmonary artery heal. Healing may be due to either alteration of local mechanical factors or nutrition of vegetations, induced by operation, and is indicated by early subsidence of clinical manifestations and laboratory evidence of infection.

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## Department of Clinical Reports

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### SUBACUTE STREPTOCOCCUS VIRIDANS ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS

SPONTANEOUS RECOVERY. RECURRENCE AFTER TWELVE AND ONE-HALF  
YEARS. RECOVERY FOLLOWING OPERATIVE TREATMENT.

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THE frequency with which subacute *Streptococcus viridans* infection becomes engrafted not only upon cardiac valves which have been previously damaged by disease but also upon pre-existing congenital defects of the heart, is too well known to require discussion. The occurrence of such infection in cases of patent ductus arteriosus constitutes one of the most common and serious complications of the latter condition. In this connection, only one case of spontaneous recovery from subacute *Streptococcus viridans* endarteritis superimposed on patent ductus arteriosus has been reported (Chester<sup>1\*</sup>). Although the use of modern chemotherapeutic methods occasionally has been followed by recovery, the results of medical treatment in general have been disappointing, and infected patent ductus arteriosus still remains an almost invariably fatal disease.

During 1940, a more radical therapeutic approach to subacute *Streptococcus viridans* endarteritis superimposed on patent ductus arteriosus was made by one of us (A.S.W.T.) and Vesell,<sup>4</sup> and in that year we reported the first case in the literature in which surgical treatment proved successful.<sup>3</sup> (The patient remains entirely well, more than two years after operation.) A second patient, operated upon almost one year ago, likewise appears to have recovered completely.<sup>5</sup>

The case herein reported is of interest for several reasons. First, it represents only the second in the literature in which a patient with patent ductus arteriosus recovered *spontaneously* from superimposed subacute *Streptococcus viridans* infection. Apropos of this, although in Chester's case<sup>1</sup> the correctness of the clinical diagnosis of patent ductus

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From The Mount Sinai Hospital, New York City.

Presented before the New York Surgical Society on Oct. 22, 1941.

\*In Chester's case, the diagnosis of patent ductus arteriosus was based upon clinical and roentgenographic evidence; and the presence of the superimposed subacute *Streptococcus viridans* infection was established by positive blood cultures. After an illness which lasted for almost one and one-half years, the patient recovered spontaneously. When last observed, two years later, she was apparently entirely free of the superimposed infection.

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arteriosus is not to be questioned, final confirmation of the precise nature of the congenital cardiovascular anomaly, either by operative or post-mortem examination, is lacking. In the present case, the diagnosis of patent ductus arteriosus was confirmed at operation, when infection recurred twelve and one-half years after spontaneous recovery from an initial episode of subacute *Streptococcus viridans* infection. The case thus becomes the first in the literature in which spontaneous recovery from infection superimposed upon a *proved* patent ductus arteriosus, occurred. Second, it appears to be the only one to be reported, in which there was recurrence after recovery from an initial infection many years previously. Finally, the case is our third of recovery from infected patent ductus arteriosus following operative treatment.

#### REPORT OF CASE

*History.*—G. O., an English-born, white woman, aged 51 years, single, and a school teacher by occupation, was admitted to The Mount Sinai Hospital on Aug. 12, 1941. She was one of five siblings, none of whom was known to have had a congenital cardiac anomaly.\* To the best of the patient's knowledge, she had not been a "blue baby." A cardiac murmur, attributed to a congenital anomaly, had been discovered early in adult life. She had had measles and pneumonia at 2, pneumonia at 14, and an operation for fistula-in-ano at 38 years of age.

Early in January, 1929, approximately twelve and one-half years before the present admission, the patient experienced lassitude, cough, and mild fever. The diagnosis of "grippe" was made. After an illness which lasted approximately one month, the symptoms ameliorated somewhat and she went to a nearby resort to recuperate. While there, weakness, lassitude, and cough again became marked. At the end of another two months, she suffered an episode of severe "pleuritic" pain in the right chest associated with dyspnea, bloody expectoration, shaking chill, and temperature of 105° F. Accordingly, she was admitted to the Atlantic City Hospital, under the care of Dr. I. Shenfeld. Shortly after admission, a blood culture was found to be positive for *Streptococcus viridans*. In view of the presence of the congenital cardiac lesion and the subsequent development of septic temperature, petechiae, and an enlarged spleen, several additional blood cultures were taken. When three such successive cultures were found to be positive, the diagnosis of subacute *Streptococcus viridans* endocarditis was made. During a three-month period of hospitalization, the temperature ranged from 98° to 99° and 102° to 104° daily, and new petechiae appeared. Splenic infarction and several episodes of pulmonary infarction also occurred. The treatment consisted of transfusions, supportive measures, and the administration of an autogenous vaccine obtained from organisms in the patient's blood. At the end of three months, she was discharged (July 15, 1929) with persisting low-grade fever.

During the next six months she was under the care of Dr. Daniel A. McAteer, of Brooklyn. During the first four of these months, the temperature ranged between normal and 101° F., and several blood cultures were positive for *Streptococcus viridans*. New petechiae appeared, and on one occasion the patient was said to have suffered an episode of renal infarction. However, during the last two months she became afebrile. (Throughout the six-month period, the treatment consisted only of

\*The patient's first cousin, by consanguineous marriage, died of subacute *Streptococcus viridans* endocarditis superimposed on patent interauricular septum and pulmonary stenosis. The diagnosis was confirmed at post-mortem examination.

the use of supportive measures.) About fifteen months after the onset of illness, she apparently had recovered to such an extent as to be able to return to work. She then remained relatively well for approximately three years.

The patient first came under the observation of one of us (L.R.T.) early in 1934 and was then suffering from mild circulatory failure. At that time, her symptoms consisted of dyspnea on moderate exertion, orthopnea, and slight cough. In the ensuing seven years, these symptoms increased slowly; but during the six months preceding admission the dyspnea became considerably more pronounced.

Four and one-half weeks before the present admission to the hospital, the patient began to complain of weakness and cough. When she first sought advice, at the end of two weeks, the temperature was found to be 100.6° F. During the next two and one-half weeks she was observed at home; dry, hacking cough and fever continued. Five days before admission, she suffered a sudden severe attack of pain in the left side of the chest associated with hemoptysis. This was attributed to pulmonary embolism with infarction. Concomitantly the temperature rose and, during the next five days, ranged irregularly between 101° and 105° F. At the end of that period (on Aug. 12, 1941), she was admitted to The Mount Sinai Hospital with the provisional diagnosis of subacute bacterial endarteritis superimposed on patent ductus arteriosus.

*Examination.*—The patient was well nourished, but slightly sallow in appearance. She did not appear acutely or chronically ill. Temperature was 101.4° F.; pulse rate, 96; respirations, 20. Dyspnea and orthopnea were present. There was no cyanosis. No petechiae were seen, and there was no clubbing of the fingers; the fundi were negative. Examination of the heart revealed no obvious enlargement at the apex, but increased widening of the area of cardiac dullness was present at the base. A very loud, "machinery-like" murmur was heard over the pulmonic area, throughout systole and most of diastole. This murmur was transmitted upward into the root of the neck. It could be heard faintly over the medial border of the left scapula. The blood pressure was 105/60. Examination of the lungs disclosed impaired resonance, diminution of breath sounds, and the presence of fine and coarse râles at the left base posteriorly.

*Laboratory Data.*—A teleroentgenogram revealed the heart to be enlarged to the left. The pulmonary conus was prominent. Moderate pulmonary vascular congestion was present. There was some clouding at the left base. The urine was negative for albumin and sugar; microscopic examination failed to reveal red blood cells or casts. Examination of the blood disclosed 4,420,000 red cells per cubic millimeter and a hemoglobin content of 86 per cent. The white blood cells totaled 6,600 per cubic millimeter, with 61 per cent segmented polymorphonuclear cells, 10 per cent nonsegmented polymorphonuclear cells, 23 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. A blood culture taken on the day of admission yielded forty colonies of *Streptococcus viridans* per cubic centimeter, after forty-eight hours' incubation.

*Preoperative Course.*—The administration of sulfapyridine was begun three days after admission. This was followed by a prompt but only temporary antipyretic effect. During the next six days, 31 Gm. of the drug were administered but then had to be discontinued because of the development of very severe nausea and vomiting. Five days later the administration of sulfathiazole was begun. This was continued for seven days without significant effect. A second blood culture, taken thirteen days after admission, disclosed the presence of fifty-two colonies of *Streptococcus viridans* per cubic centimeter. By the nineteenth hospital day, the hemoglobin content of the blood had fallen to sixty-two per cent and the patient's general physical condition had deteriorated considerably. Dr. Emanuel Libman saw her

in consultation at that time and, because of the general downhill course and the failure of chemotherapy to influence the infection, concurred in the opinion to proceed with surgical therapy. As in the two previous successful operative cases reported by one of us (A.S.W.T.), the relatively short duration of infection and the lack of evidence of valvular involvement and *peripheral* embolization appeared to render the case suitable for such treatment.

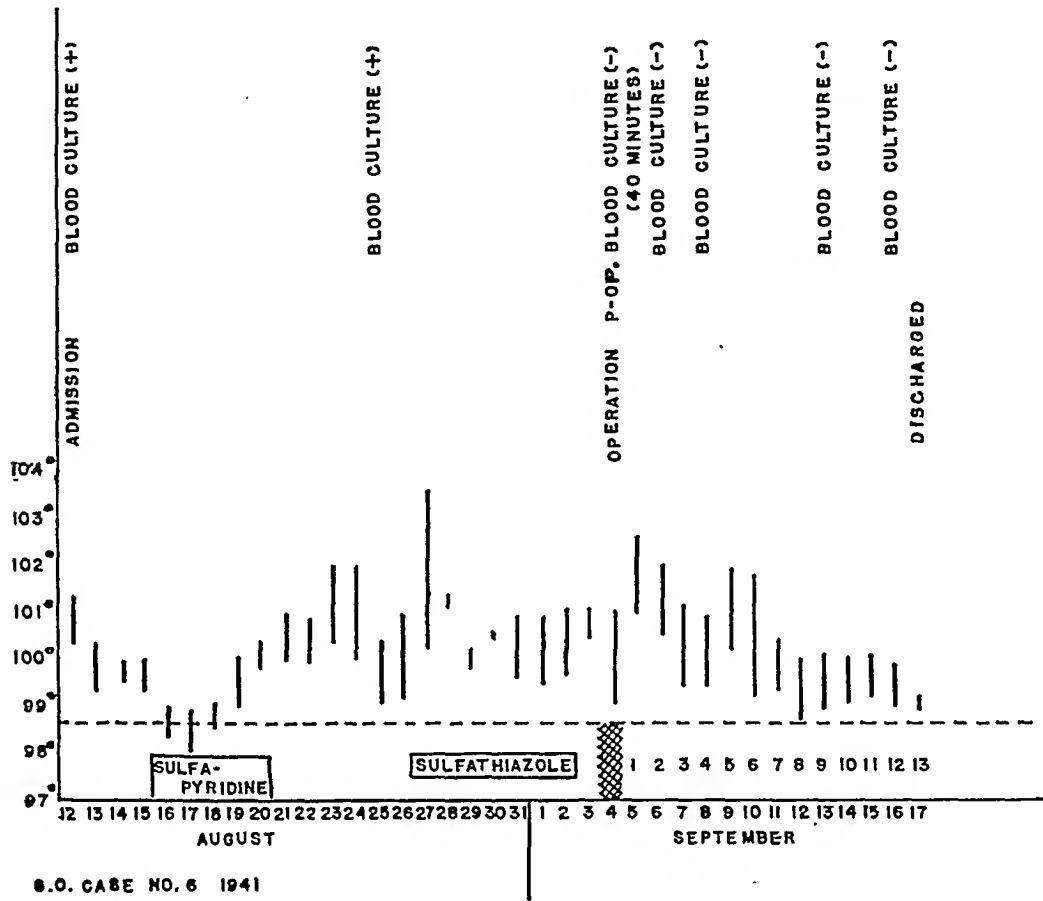


Fig. 1.

*Operation.*—On Sept. 4, 1941, twenty-three days after admission (or approximately eight weeks after the onset of infection), operation was performed (by A.S.W.T.) under avertin-ethylene anesthesia. The operative technique which was employed has been reported elsewhere<sup>2</sup> and therefore will not be described here. A brief description of the operative findings follows: Extensive adhesions were present between the lung and thoracic parietes, mediastinum, and pericardium. A visible tremor was noted over the base of the heart; a localized thrill was palpable over the region of the pulmonary artery. The aorta measured about 1 inch in diameter, and the pulmonary artery, about 1½ inches in diameter. Several inflamed lymph nodes and some edematous areolar tissue were present in the region between the undersurface of the aortic arch and the upper portion of the trunk of the pulmonary artery. The ductus measured approximately ¾ inch long and ⅜ inch in diameter. When the ductus was compressed the thrill within the pulmonary artery and ductus ceased at once, the cardiac rate became appreciably slower, and the visible tremor of the heart disappeared. At the commencement of operation, the pulse rate was 102 and the blood pressure, 122/82. After double ligation of the ductus, the pulse rate was 86 and the blood pressure, 118/86. The duration of operation was fifty-five minutes.

*Postoperative Course.*—The postoperative course was relatively uneventful. The highest temperature recorded was 102.8° F. on the day following operation. Thereafter it receded, and after the eighth postoperative day it remained under the 100° level. By the thirteenth day the temperature was essentially normal. The cardiac murmur disappeared immediately after operation. The wound healed kindly, the skin clips being removed on the fourth postoperative day. Two days later, the silk retention sutures were removed and a small collection of serum was evacuated from the superficial wound. Serosanguineous fluid was aspirated from the left side of the chest on the third and fifth postoperative days, respectively. The patient was permitted out of bed on the ninth day and was discharged on the thirteenth day following operation.

The first postoperative blood culture was taken forty minutes after operation,\* and the succeeding cultures, on the second, fourth, ninth, and twelfth postoperative days respectively. All remained sterile throughout fourteen days of incubation. No chemotherapy was administered postoperatively. At the time of discharge from the hospital the patient felt well, was gaining strength rapidly, and appeared to be in good physical condition. Since then she has improved progressively. At the present time, approximately nine months after operation, all evidence of circulatory failure has disappeared, and the clinical manifestations of infection remain absent.

#### SUMMARY

A 51-year-old female with patent ductus arteriosus, suffered an episode of subacute *Streptococcus viridans* endarteritis twelve and one-half years previously. At the time, the diagnosis of a congenital cardiac lesion was based upon the absence of a history of rheumatic fever and the presence of a characteristic murmur, known to be of long duration. The diagnosis of superimposed infection rested upon the presence of irregular fever, chills, malaise, splenic enlargement, petechiae, and several episodes of pulmonary infarction, and was confirmed by blood cultures which repeatedly were positive for *Streptococcus viridans*. The treatment consisted of repeated blood transfusions, supportive therapy, and injections of an autogenous vaccine. After an illness of approximately fifteen months, she apparently recovered completely.

The patient first came under the observation of one of the authors, with symptoms of mild circulatory failure, approximately eight years prior to the present admission. During the ensuing years the circulatory symptoms increased slowly but progressively. Approximately four and one-half weeks before admission to the hospital, clinical manifestations of superimposed infection, similar to those present twelve and one-half years previously, reappeared. During a twenty-three-day period of hospital observation, the clinical course was progressively downhill. The administration of both sulfapyridine and sulfathiazole was without significant effect; and blood cultures revealed as many as fifty-two colonies of *Streptococcus viridans* per cubic centimeter. Operation was performed primarily for the purpose of eliminating the infection. The procedure consisted of double ligation of the ductus, by a modification of technique devised by one of the authors. A blood culture taken

\*The remarkable rapidity with which organisms disappear from the blood stream will be discussed in detail in a forthcoming communication.

forty minutes after operation was sterile throughout fourteen days of incubation. Four blood cultures were taken subsequently, and these likewise were negative. Chemotherapy was not administered during the postoperative course. Approximately nine months have elapsed since operation. All manifestations of infection and of circulatory failure remain absent, and the patient is in better health than in many years.

This is the first case of spontaneous recovery from subacute *Streptococcus viridans* infection superimposed upon a *proved* patent ductus arteriosus. It also is the first case of infected patent ductus in which, after recovery from an initial episode, the infection recurred. Finally, it is our third, in which operation upon a patent ductus arteriosus has been followed by recovery from infection.

The authors are greatly indebted to Dr. Shenfeld and Dr. McAteer, for information concerning the patient while she was under their care.

NOTE: Since this report was submitted for publication, three additional cases of infected patent ductus arteriosus have been operated upon successfully (by A.S. W.T.).

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Renal Hypertension. *Am. J. Physiol.* 135: 361, 1942.

Hypertension due to renal arterial compression or compression of the renal parenchyma in perinephric scar may occur without constant or persistent changes in the renal clearances of diodrast, phenol red, inulin, or urea and without significant abnormalities of tubular excretory or reabsorptive capacity and, therefore, probably in the absence of ischemia of excretory renal tissue.

Measurements of total renal blood flow from the clearances and extraction percentages of phenol red and inulin indicate no correlation of mean arterial pressure with the rate of renal blood flow and establish the persistence of hypertension in the absence of renal ischemia. Evidence of renal vasoconstriction, predominantly of the efferent arterioles, was obtained from the levels of inulin extraction and renal blood flow in some dogs during phases of more severe hypertension and in association with secondary renal ischemia. In one dog in which hypertension was the result of perinephritis, intraglomerular filtration pressure was increased in the absence of changes in "effective renal blood flow." Ischemia due primarily to compression or occlusion of the renal artery was usually associated with decreased renal extraction of inulin, due apparently to decreased filtration pressure.

The persistence of experimental renal hypertension in the absence of renal ischemia is consistent with the view that intrarenal reduction of pulse pressure rather than ischemia may be the effective cause of experimental renal hypertension.

AUTHORS.

Heinbecker, P., and Barton, W. A.: An Effective Method for the Development of Collateral Circulation to the Myocardium. *Ann. Surg.* 114: 186, 1941.

An effective method of producing a collateral circulation for the dog's myocardium is described.

The effectiveness is proved by the fact that, following complete ligation, at one operation, of the anterior descending and left circumflex branches of the left coronary artery approximately 1 cm. from the aorta, six of fourteen dogs survived. In control animals, such ligations were immediately fatal.

At autopsy the heart muscle of the surviving animals showed no gross infarction.

On the basis of the experimental evidence, it is felt that, for a maximally effective collateral circulation to the heart, the extrinsic source should contain blood vessels of large caliber.

The method should be applicable to the treatment of myocardial ischemia in man.

AUTHORS.



White, P. D., Adams, F. D., and Craib, D.: A Note on Cardiac Murmurs. Recommendation for a Revised Terminology. *Am. J. M. Sc.* 203: 52, 1942.

The true nature of the various types of murmurs is more clearly indicated by the following nomenclature:

*Physiologic Murmurs*.—A. Intracardiac or intravascular. B. Extracardiac. (a) Cardiopulmonary. (b) Pericardial.

*Pathologic Murmurs*.—A. Due to structural valvular disease. B. Due to congenital cardiovascular defects. C. Due to dilatation of ventricles or aorta or pulmonary artery from: (a) Cardiovascular disease. (b) Other diseases, such as anemia, thyrotoxicosis, or severe infection. D. Due to pericarditis.

AUTHORS.

Levin, E.: Action of Mercurial Diuretics on Blood Volume. *Rev. argent. de cardiol.* 8: 267, 1941.

Blood volume determinations were made in thirty-five patients with the Congo red method before and one or two hours after the administration of mercurial diuretics. Five of the eight nonedematous patients showed an increase of blood volume after the administration of diuretics; in four noncardiac edematous patients an even greater hypervolemia was detected. On the other hand, hypervolemia was seen in only a few of the cardiac edematous patients, most of them showing iso- or hypovolemia. The patients who had hypovolemia after the administration of diuretics had been previously digitalized.

The author suggests the advisability of previous digitalization to prevent the hypervolemia which might occur after the administration of mercurial diuretics.

AUTHOR.

Levine, S. A.: Auscultation of the Heart. *New England J. Med.* 225: 526, 1941.

Even a simple and time-honored custom and diagnostic procedure is subject to review and criticism in order to restate its principles, its practices, the interpretation of findings, and its value. Bedside medical physical diagnosis remains still an important part of cardiology and auscultation as one of the methods. The author treats the subject simply, and the article is good reading.

McCULLOCH.

Burton, S. D., and Mehlman, J. S.: An Unusual P-Wave in Chest Lead CF<sub>2</sub> Following Spontaneous Pneumothorax. *J. Lab. & Clin. Med.* 27: 465, 1942.

A case is presented showing an unusual and deeply inverted P wave of 14 mm. in Lead CF<sub>2</sub>. This P wave was produced by cardiac displacement, resulting from a spontaneous pneumothorax which brought the right auricle into close apposition to the anterior chest wall. The contour of the P wave was such as to suggest that the part of the auricle beneath the chest contained the pacemaker, the sinus node. As the pneumothorax was relieved, the large P wave became diphasic, suggesting the apposition of other parts of the auricle to the anterior chest wall. Finally, as further resolution of the pneumothorax progressed, the P wave returned to its smaller and more nearly normal appearance, which existed before the pneumothorax occurred. During the period of pneumothorax, the changes in the P wave with change in body posture indicated greater than normal mobility of the heart.

AUTHORS.

Evans, W.: Chest Lead ( $CR_1$ ) Electrocardiograms in Auricular Fibrillation. Brit. Heart J. 3: 247, 1941.

The chest electrocardiogram,  $CR_1$ , was taken in sixty patients with auricular fibrillation in order to study the auricular wave. Large and conspicuous waves, resembling those of auricular flutter, were found in thirty-nine patients (Type I). In the remaining twenty-one cases (Type II) the auricular waves were small and no more conspicuous than in many limb lead electrocardiograms.

No factor was discovered that determined in a patient with auricular fibrillation whether the auricular movements would be represented in the  $CR_1$  cardiogram by large or by small waves, except that, if the ventricular rate was high and the auricular oscillations were conspicuous in the limb lead cardiogram, distinct waves were likely to show in the  $CR_1$  cardiogram. The etiology and the duration of the arrhythmia, the size of the right auricle, digitalization or its absence, and the thickness of the chest wall did not seem to decide whether a patient would exhibit large (Type I) or small (Type II) auricular waves.

The features of the auricular waves were clearly shown in those patients classified as Type I, and these were specially studied. The form of the waves, varying slightly in different patients, resembled the waves found in auricular flutter although they lacked the same constant pattern. The waves recurred continuously without a pause at the isoelectric level, and each showed a gradual upstroke followed by a steeper downstroke. The amplitude of the wave was occasionally subject to a natural variation, and this was independent of any known extrinsic factor, including respiration. Small waves were often bifid, thereby giving the appearance of two waves and explaining the more frequent oscillations seen in the limb lead cardiogram. The wave was no larger in mitral stenosis than in nonrheumatic auricular fibrillation.

The rhythm of the auricular waves was slightly irregular in eighteen patients, regular in thirteen except for interruptions by ventricular systole when the succeeding auricular wave was as often delayed as quickened, and quite regular in six cases, in which the rhythm was undisturbed even by ventricular systole, so that the tracing closely resembled that of auricular flutter.

The frequency of auricular waves in auricular fibrillation was found to be reasonably constant; the rate was 375 to 400 per minute in more than half the cases; with two exceptions the range was 350 to 450, and the average rate for all patients was 400. Higher rates of auricular contraction generally assigned to auricular fibrillation have been based on observations on limb lead cardiograms which often contain more than one oscillation representing a single beat of the chest lead cardiogram. The rate was uninfluenced by digitalis, but it was reduced by quinidine.

In two patients in whom a clinical diagnosis of auricular fibrillation was supported by a limb lead cardiogram, the  $CR_1$  tracing demonstrated auricular flutter in one and 2:1 auriculoventricular block in the other. The value of this chest lead is also seen in elucidating cases of so-called impure flutter, better regarded as fibrillation, and in the interpretation of records with auricular waves in the limb lead cardiogram sometimes subdued or obscured, as in heart block and in paroxysmal tachycardia.

The chest  $CR_1$  cardiogram permits the limited definition of auricular fibrillation as a succession of waves at the rate of about 400 per minute, differing slightly in size and shape, and with a rhythm which is regular almost as often as it is irregular. The ventricular responses in fibrillation have no constant relationship to the auricular waves, probably because the auricular rate is too high for any regular control.

In contrast auricular flutter shows a succession of waves at a rate of about 300 per minute, identical in size and shape, and perfect in rhythm. The ventricular responses in flutter are determined by the auricular waves giving a fixed or varying ratio.

AUTHOR.

**Wearn, J. T.:** Morphological and Functional Alterations of the Coronary Circulation. Bull. New York Acad. Med. 17: 754, 1941. Harvey Lecture, New York Academy of Medicine.

The author reviews his work with the coronary vascular system during the past ten years. He presents an important recapitulation of this work and our present knowledge of the subject.

McCulloch.

**Green, C. A.:** Observations on the Antistreptolysin O Titre in Relation to the Mechanism of Acute Rheumatic Fever. J. Path. & Bact. 53: 223, 1941.

The antistreptolysin O titers of 1,346 sera from male adolescents, including various clinical groups and healthy subjects, have been determined.

The mean titer in normal controls was 79; in 82.3 per cent of the sera the titer was less than 125 units.

An increase in titer was invariably noted in scarlatina, the mean being raised to 300, with maximum titers occurring in the third and fourth weeks of infection.

Simple pharyngitis due to *Streptococcus haemolyticus* was usually but not always followed by a rise in titer, the mean being 263.

The mean titer in the active phase of acute rheumatism was 444 and during the inactive phase 210.

Of 110 attacks of acute rheumatism, 79.9 per cent were accompanied by a significant increase in titer which, in the majority of cases, reached maximum proportions at or just after the height of clinical activity; in 10.1 per cent of the attacks no change in titer was observed, and in 3.6 per cent the titers were reduced during the active phase.

Examples of the various types of antistreptolysin O response in rheumatic and non-rheumatic subjects are described.

AUTHOR.

**Ragan, C., and Bordley, J., III:** The Accuracy of Clinical Measurements of Arterial Blood Pressure, With a Note on the Auscultatory Gap. Bull. Johns Hopkins Hosp. 69: 504, 1941.

The commonly employed clinical method of measuring blood pressure should not be looked upon as a truly accurate procedure. In most adult subjects it provides reasonably reliable information, but in a significant number of cases the information may be misleading. Misinformation is particularly likely to be obtained in subjects with unusually large or unusually small arms. If the arm is small, the clinical estimate of the systolic pressure is likely to be too low. If the arm is large, the clinical estimate of both systolic and diastolic pressure is likely to be too high. The error in either direction may exceed 30 mm. Hg.

The foregoing observations must be borne in mind whenever it is necessary to come to a decision concerning the diagnostic or prognostic significance of minor depressions or elevations in the level of the blood pressure.

Statistical studies of the relation between blood pressure and body weight should take into account the influence of the circumference of the arm upon the accuracy of the blood pressure measurements.

AUTHORS.

Friedman, M., Selzer, A., Kreutzmann, H., and Sampson, J. J.: The Changes in the Blood Pressure and in the Renal Blood Flow and Glomerular Filtration Rate of Hypertensive Patients Following Unilateral Nephrectomy. *J. Clin. Investigation* 21: 19, 1942.

The total diodrast clearance was found to be reduced in four of five patients having unilateral kidney disease with hypertension. It was more reduced in the affected kidney than in the normal one. The total inulin clearance was diminished in two and normal in the remaining three patients.

The removal of the diseased kidney was followed by an increase in the renal blood flow and in the glomerular filtration rate of the remaining kidney in all five patients.

There was a significant blood pressure reduction in three of the five patients, but in none was there a complete return of the blood pressure to normal when last examined, despite the fact that in three of these patients there was no ischemia of the remaining kidney.

AUTHORS.

Goldblatt, H., Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension. XV. Experimental Observations on Hypertension Associated With Unilateral Renal Disease; Effect of Occlusion of the Ureter on Experimental Hypertension Due to Unilateral Renal Ischemia. *Arch. Surg.* 43: 327, 1941.

Constriction of one main renal artery in the dog causes a variable rise of blood pressure, which persists for a variable period. Excision of the ischemic kidney results in a prompt fall of the blood pressure to normal. Similarly, in man, hypertension may be associated with unilateral renal disease, presumably producing ischemia, and removal of the diseased kidney results in a fall of the blood pressure to normal if the other kidney is normal.

Occlusion of one ureter in the dog does not result in elevation of blood pressure. Occlusion of the ureter performed at the same time that the main artery of the same kidney is constricted interferes with the development of the elevated blood pressure of a dog with unilateral renal ischemia. After the blood pressure has become elevated owing to constriction of one main renal artery, occlusion of the ureter of the same kidney causes a fall of blood pressure to normal within three to seven days. Constriction of both main renal arteries accompanied with occlusion of both ureters usually results in a moderate elevation of blood pressure, which persists until death of the animal in uremia. Occlusion of the ureter and constriction of the main artery of one kidney followed by contralateral nephrectomy also usually result in a moderate elevation of blood pressure, which persists until death occurs in uremia. A hypertensive effect is, therefore, produced by kidneys with the main artery constricted and the ureter occluded when no normal kidney is present.

A vasoconstrictor effect has been obtained (by the L  wen-Trendelenburg technique) with citrated plasma of the venous blood of kidneys with the renal artery constricted and the ureter occluded, although the blood pressure of the animals was not elevated. No vasoconstrictor effect, but rather a dilator effect, was obtained with the plasma of venous blood from the contralateral, normal kidney and with the plasma of systemic venous blood. This indicates that the effect of occlusion of the ureter on a kidney with the main artery constricted is not to abolish the production

of pressor substance but to interfere with the rate of entrance of pressor-producing substance from the kidney into the systemic circulation or diminish the amount produced. In either case, the failure of the blood pressure to become elevated as a result of the decreased amount of pressor-producing substance which enters the systemic circulation may also be due to the neutralizing effect of the contralateral normal kidney.

Although some human beings have already been described in whom excision of a kidney with the ureter completely obstructed or of a kidney from which no urine was obtained was followed by a return of the blood pressure to normal, the experiments indicate that this may not prove to be the rule and that in such cases excision of the kidney should be undertaken for the main purpose of removing the diseased organ rather than for possible cure of the hypertension. In all cases of contemplated unilateral nephrectomy it is desirable, with the limited means available at present, to determine that the other kidney is, as far as can be determined, normal, before removing an obviously diseased, though still functioning, kidney for the possible favorable effect of this procedure on the elevated blood pressure.

AUTHORS.

Glen, A. M. Temporary Vascular Occlusion Ending Fatally in Uremia. *Brit. M. J.* ii: 875, 1941.

This is a case of central dislocation of the hip with fracture of the pubic rami of the same side causing obstruction of the external iliac vessels. Relief of the obstruction by dividing the inguinal ligament was followed by sudden and profound collapse comparable to that resulting from the sudden release of a tourniquet left over-long in position.

Death resulted from uremia within four days of the accident, and the microscopic appearances of the kidneys corresponded closely with those recently described in cases of crush injury (Bywaters and Beall, 1941; Beall, Bywaters, Belsey, and Miles, 1941; Mayon-White and Solandt, 1941).

The hardness of the limb noticed after operation is interesting in view of the theory recently put forward by Patey and Robertson (1941) that the syndrome may be due to loss of substances from the circulation into the injured limb. Unfortunately no particular attention was paid to this aspect at the time.

It is hoped that the findings described may prove of interest to those investigating such cases and to others who may have to deal with similar injuries.

AUTHOR.

Felsen, J.: Intestinal Vascular Sclerosis. *J. Lab. & Clin. Med.* 27: 576, 1942.

The association of intestinal vascular sclerosis with long-standing hypertension is quite constant. In the reviewing of 1,000 necropsies at the Bronx Hospital from the standpoint of concomitant intestinal vascular sclerosis and generalized arteriosclerosis in the same person, agreement was found in all instances where advanced changes were present in the larger vessels.

Intestinal vascular sclerosis is essentially a disease of old age. The chief symptoms are distention, constipation, indigestion, and abdominal cramps. Therapy consists of cardiovascular supportive measures, an easily assimilated diet, intestinal aspiration, and intestinal oxygenation.

AUTHOR.

Bauer, G.: Venous Thrombosis: Early Diagnosis With the Aid of Phlebography and Abortive Treatment With Heparin. *Arch. Surg.* 43: 462, 1941.

For successfully combating thromboembolic disease two measures are necessary—early diagnosis and immediate energetic treatment with heparin.

Phlebography permits of an earlier diagnosis than any other known method. With its aid the first manifestations of the disease in the lower part of the leg can be revealed.

If in this stage regular treatment with heparin is started, almost ideal results can be expected, for the whole disease often takes an abortive course.

In twenty-one cases in which the diagnosis of an early stage of thrombosis in the lower part of the leg was confirmed by phlebographic examination, the patients were treated with heparin, 100 mg. three times daily for three to five days. All of the patients recovered and were ambulatory within a few days.

In thirty-two similar cases in which treatment with heparin was not used, two patients died, three had pulmonary embolism, eight had pulmonary infarct, and in twenty-four the thrombosis spread to the femoral veins. The average length of confinement to bed was forty-three days.

AUTHOR.

Marvin, H. M.: Newer Surgery of the Heart and Large Vessels: Medical Aspects. *Bull. New York Acad. Med.* 17: 737, 1941.

The author believes that, of the operations mentioned, those designed to provide the heart with a new source of blood are probably valueless. Surgical ligation of the patent ductus arteriosus seems destined to be of great importance in a group of patients that will probably always be numerically small. Total thyroidectomy may have a limited place, but in the absence of an elevated basal metabolic rate the indications for it are not very clear and the results are apt to be unsatisfactory. Alcohol injections into the thoracic sympathetic ganglia have been proved to be highly satisfactory by years of experience. The Brauer operation for adhesive mediastinopericarditis seems to me to be of demonstrated value in a few cases, and I believe the time has not come to discard it. Pericardiectomy for constrictive pericarditis may be confidently regarded as a major therapeutic procedure and a brilliant surgical contribution.

AUTHOR.

Fine, J., and Sears, J. B.: The Prophylaxis of Pulmonary Embolism by Division of the Femoral Vein. *Ann. Surg.* 114: 801, 1941.

Thrombosis of the deep veins of the lower leg is the focus of the origin of the great majority of pulmonary emboli.

Pulmonary embolism until recently has been regarded as a dramatic postoperative catastrophe for which adequate prophylactic or therapeutic measures are not available. This is no longer tenable except in the case of massive embolus which has occurred in the absence of detectable signs of venous thrombosis of the lower leg and in the absence of a previous episode of embolism.

If the surgeon will conscientiously observe the patient from the very beginning and throughout the postoperative period for the signs and symptoms of phlebitis in the deep veins of the lower leg, he is likely to discover the existence of at least suspicious evidence of phlebitis in a much larger number of instances than heretofore in advance of the discharge of an embolus.

If the evidence of phlebitis in the lower leg is clear-cut, immediate division of the femoral vein below or above the profunda should be done (bilaterally if both legs are

involved). If embolism has not yet occurred, the procedure may be considered a justifiable prophylactic measure. If an embolus has been discharged, however massive it may be, so long as it is not fatal, immediate division of the femoral vein is the one most effective measure remaining to prevent the discharge from its commonest source of still another embolus which may prove fatal.

If the evidence of phlebitis is only presumptive, a decision can be reached by the venographic technique of Bauer.

If embolism has occurred in the total absence of signs or symptoms of phlebitis, the process will usually be demonstrated and lateralized by the venographic technique of Bauer. An embolus henceforth can be assumed to have arisen from the pelvic or other inaccessible veins only when no involvement of the deep veins of either lower extremity is shown to exist by employment of this technique.

There is no good evidence that division of the femoral vein involves any significant immediate risk or adds to the disability created by the phlebitis itself. On the contrary, aside from its prophylactic value for embolism, division appears to exert a favorable influence on the course of the disease probably because of the concomitant disruption of some of the pathways involved in the accompanying vasospastic reflexes.

Because pulmonary infarcts and fatal pulmonary embolism due to phlebitis of the lower leg occur frequently in nonsurgical as well as surgical patients, the therapeutic problems involved become the common concern of the internist as well as the surgeon.

AUTHORS.

Jackson, B., and Wald, G.: Action of Thiamine and Cocarboxylase on Frog Ventricle. *Am. J. Physiol.* 135: 464, 1942.

Experiments are reported upon the action of thiamine (vitamin B<sub>1</sub>) and of its pyrophosphate ester (cocarboxylase) upon the Straub preparation of the frog heart. This is a ventricular preparation, in which test solutions act directly upon the heart muscle and produce changes only in the amplitude of the beat.

Between pH 6.0 and 5.2 thiamine  $10^{-3}$  by weight progressively depresses the beat to a complete stoppage. At a concentration of  $10^{-4}$  this effect is still observed; at  $10^{-5}$  it has become negligible. Cocarboxylase  $10^{-3}$  behaves similarly but continues to depress the beat 10 to 25 per cent up to pH 7.6.

This action is independent of that of acetylcholine. Atropine, which completely abolishes the latter, has no effect upon the former. Further, the depressions produced by thiamine or cocarboxylase and by acetylcholine are simply and accurately summated when both types of substances are applied to the heart simultaneously.

Above pH about 6.0 thiamine  $10^{-5}$  to  $10^{-3}$  progressively antagonizes the action of acetylcholine. This effect is not exhibited by cocarboxylase. Depression of the heartbeat and acetylcholine antagonism therefore appear in these experiments under mutually exclusive conditions; thiamine shifts from the first to the second type of activity at pH about 6, while cocarboxylase, which depresses the beat at all pH's investigated, does not antagonize acetylcholine at all. The shift in behavior of thiamine with pH may be related to its change from a monoacidic to a diacidic base at pH's below 6. The significance of these effects in the intact animal cannot yet be evaluated.

AUTHORS.

Lowe, T. E.: Blood Pressure Changes Following Localized Myocardial Death. *M. J. Australia* 11: 447, 1941.

It is possible to produce localized areas of necrosis in cardiac muscle, at predetermined sites and of controlled extent, by the injection of small amounts of concentrated phenol solutions.

These observations show that the destruction of localized areas of cardiac muscle, of the sizes indicated, produces no permanent disturbance of systemic blood pressure immediately after destruction, irrespective of the particular muscle bundle involved.

These experiments yield no clue to the causal factors of the fall of blood pressure observed, at least in later periods, by clinicians and experimental workers.

AUTHOR.

Cuykendall, M.: *The Incidence of Heart Disease in the University Student Age Group*. New York State J. Med. 41: 2037, 1941.

In the university student age group the rheumatic state has already produced anatomic change in practically all hearts susceptible to this change, but the syphilitic and degenerate heart diseases of middle life have not yet occurred. A survey of the incidence of heart disease was conducted among the 6,489 students in attendance at Cornell University during the academic year in 1938 to 1939.

In previous surveys wide variations in the incidence of heart disease result from lack of uniformity in the compilation of material. Some surveys include one or more of the various subheadings of etiological or physiologic diagnosis. Further variation in the reported incidence is due to confusion in the differentiation of the systolic murmur. In the present survey the anatomic diagnosis is considered to be the only diagnosis of organic disease. However, certain of the etiological and physiologic diagnoses with their incidence among Cornell University students are briefly noted so as to make possible a comparison with those surveys which include these additional conditions.

Organic heart disease was diagnosed in 1.5 per cent of the Cornell students, i.e., 1.10 per cent of the men and 3.0 per cent of the women. The rheumatic type of heart disease comprised 82 per cent of the organic heart disease in this group and was present in 1.2 per cent of the students. The mitral valve was involved in 90 per cent of the rheumatic hearts. Rheumatic heart disease was present in 2.6 per cent of the women and 0.8 per cent of the men students, a sex incidence ratio of 3:1.

Rheumatic heart disease is the most common type of heart disease present among the Cornell University students. Factors that are known to influence rheumatic heart disease—namely, age, sex, economic environment, prevalence of the rheumatic state in the community, and race—are found in general to exert the expected influence. An exception, however, is the influence of sex; the ratio of three times as much rheumatic heart disease among the women students as among the men is much greater than in any previously reported survey.

AUTHOR.

Keys, A., and Viola, A.: *The Cardio-Circulatory Effects in Man of Neosynephrin (1- $\alpha$ -Hydroxy- $\beta$ -Methylamino-3-Hydroxy-Ethylbenzene Hydrochloride)*. J. Clin. Investigation 21: 1, 1942.

The threshold dosage of neosynephrin in the average adult is about 2 mg. subcutaneously, 0.4 mg. intravenously, and 50 mg. orally. The threshold effect is a decline in pulse rate and usually a slight increase in blood pressure.

The average dosage of neosynephrin for satisfactory pressor and cardiac effect is about 5 mg. subcutaneously, 0.8 mg. intravenously, or 250 mg. orally. With these dosages the pulse rate declines 15 to 35 beats per minute, the systolic blood pressure rises 15 to 40 mm., and the diastolic blood pressure rises 10 to 30 mm.

The upper limit for safe and comfortable dosage of neosynephrin in normal adults is about 10 mg. subcutaneously, 1.5 mg. intravenously, and 300 mg. orally.



With rare exceptions no sensation or symptoms other than pilomotor excitation are elicited by dosages below these levels.

Neosynephrin increases the positivity of the T wave, decreases that of the P, and prolongs the diastolic pause; otherwise the electrocardiogram is essentially unchanged. Cardiac irregularities, extrasystoles, and escape phenomena do not occur except in rare cases with the largest doses.

Neosynephrin produces an increase in the size of the heart in both diastole and systole. The stroke output of the heart is increased, but the minute output of the heart is generally somewhat decreased. There is a slight prolongation of the circulation time and a slight increase in venous pressure. The total work of the heart is increased.

In the atropinized subject the pressor effect of neosynephrin is augmented and tachycardia is produced. The same result is obtained in vagotomized animals and in the isolated or denervated heart.

Tachycardia of sinus origin is readily controlled with neosynephrin, but tachycardia of ventricular or supraventricular origin is not affected. Sinus bradycardia responds to neosynephrin with a further decrease in pulse rate.

Neosynephrin differs from epinephrine in its small pressor and cardiac potency, its longer duration of action, and its stimulatory effect on some of the parasympathetic effectors, notably those of the cardiac vagus.

AUTHORS.

**Dauber, D., Landowne, M., Katz, L. N., and Weinberg, H.: Effects of Interrupting and Restoring the Circulation to the Lower Extremities. J. Clin. Investigation 21: 47, 1942.**

The phenomena associated with the application and release of constricting tourniquets were observed.

Cardiac acceleration followed release of occluding cuffs about the lower extremities in normal subjects. This was absent or reduced in patients with thromboangiitis obliterans.

A fall in the blood pressure was caused by the opening of a temporary low-resistance pathway for blood through the dilated vessels resulting from the previous occlusion of the limbs.

Evidence is cited to prove that the primary mechanism inducing the cardiac acceleration is a reflex response to the drop in pressure in the central arteries (Marey's law).

The evidence presented also indicates that the cardiac acceleration is not caused by a metabolite accumulating in the constricted extremities and that it is not satisfied by the assumption that the reflex arises from the occluded vessel or from the tissue of the extremity.

AUTHORS.

## Book Reviews

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PRE-ECLAMPTIC AND ECLAMPTIC TOXEMIA OF PREGNANCY: By Lewis Dexter, A.B., M.D., Soma Weiss, A.B., M.D., and Collaborators. Little, Brown & Co., Boston, Mass., 1941, 415 pages.

There is some evidence that as pregnancy advances the blood pressure tends to increase. If this increase exceeds normal limits it is called pre-eclampsia. In all demonstrable respects, pre-eclampsia resembles essential hypertension, except that it occurs with pregnancy, in most cases disappears after delivery, and is often associated with, or preceded by, water retention. This feature may be part of the pregnancy, which tends to be associated with water retention, also without increase of blood pressure. In women who have had increased blood pressure during pregnancy, the incidence of cardiovascular renal disease in later life is greater than normal. Among middle-aged women with hypertension the incidence of hypertension during past pregnancies is greater than normal. If a woman has increased blood pressure during one pregnancy, her chances of having elevated blood pressure during a subsequent pregnancy are increased, although this may not happen.

There is also some evidence that patients whose blood pressure is increased during pregnancy show a greater than normal incidence of hypertension in their families and a tendency to constitutional features which are often associated with hypertension. These are statistical studies showing merely a trend. There remain many women who have increased blood pressure during pregnancy, but show no other evidence indicating a constitutional predisposition to hypertension.

When patients with essential hypertension become pregnant, the blood pressure may remain unaffected or increase, or, in a few cases, return to normal and remain there for the duration of the pregnancy, to rise again after delivery. Thus, the effect of pregnancy on pre-established hypertension is unpredictable.

There is, then, a relation between the increase of blood pressure in pregnancy and essential hypertension, but all attempts to define this relation have so far failed. Four general factors which must be considered are (1) the patient, apart from any constitutional tendency she may have toward an increase in blood pressure, (2) a specific factor in the patient predisposing her to increase in blood pressure ("hypertensive diathesis"), (3) the pregnancy, apart from any specific blood pressure raising factor, and (4) a specific blood pressure increasing factor of pregnancy.

Any attempt to explain the increase of blood pressure during pregnancy must fall into one of three groups.

*Group I.*—Factor 4 appears as a complication of pregnancy, irrespective of the patient's susceptibility to hypertension (Factor 1). This explanation ignores all the facts mentioned above, except the one that the blood pressure may rise during pregnancy in a patient who manifests no other evidence of a hypertensive diathesis. This, however, does not rule out its presence.

*Group II.*—Normal pregnancy activates or accentuates hypertension in patients predisposed thereto (Factor 3 and Factor 2). This explanation fits most cases but ignores (1) those in which an already elevated blood pressure is not further raised,

and (2) the fact that increased blood pressure in one pregnancy may be followed by normal blood pressure in a subsequent one.

*Group III.*—A specific, blood pressure raising factor (Factor 4) in pregnancy acts in persons who have a latent or demonstrable tendency to hypertension (Factor 2). This explanation conforms, I believe, to all the established facts, and practically covers the authors' thesis that toxemia of pregnancy is a *condition sui generis* (p. 8), but that it occurs more easily in those who have a constitutional predisposition (p. 297).

Beyond this the authors become increasingly speculative. Because the manifestations of toxemia often persist if the ovum is retained in the uterus after the fetus has died, they believe that the placenta must (or may?) be responsible for their persistence, but, in spite of diligent search both by experiment and in the literature, they fail to suggest any substance or mechanism which could explain this function.

Their hypothesis is further weakened by the fact that they must assume the probability of a second missing link, for there is no evidence that any placental secretion directly affects the blood pressure. The authors thoroughly investigate all possible mechanisms whereby the blood pressure may be raised. The many observations on hepatic changes during pregnancy and the evidence that an antidiuretic substance may cause water retention and edema of some vital structures (perhaps parts of the brain) are interesting. In such cases an increase in blood pressure might be a compensatory mechanism.

Apparently, the authors would consider these the high lights of their book, but in addition they have reported a number of largely negative, original researches on the pressor substances in the pituitary gland, in the placenta, and on other hormones. These are also a complete clinical and pathologic discourse on the known facts of toxemia of pregnancy, and a chapter on the treatment in which they, naturally, lean heavily on the authority of Stroganoff and of Dieckmann and on the established routines of the Boston Lying-in Hospital.

The book constitutes an important contribution to the subject of toxemia, but it lays itself open to many criticisms which should not be necessary. It is poorly arranged, and its purpose is not immediately obvious. After a few introductory chapters the reader is detoured through a number of chapters which are given disproportionate prominence, apparently because they constitute the authors' original research contributions. Then follows the chapter on pre-eclamptic and eclamptic toxemia which is the purpose of the book. This chapter is without proper subdivisions or equivalent headings. Too often the authors disregard English syntax. However, the book is well printed and contains remarkably few misprints.

JULIUS JENSEN.

ANOXIA; ITS EFFECT ON THE BODY: By Edward J. Van Liere, Ph.D., M.D., Professor of Physiology, West Virginia University. University of Chicago Press, 1942, 269 pages, 17 illustrations, \$3.00.

This is a review of the effects of anoxia, produced chiefly by high altitude or chamber experiments, on the physiologic functions of men and animals. It is timely and of direct importance to those who are working in aviation medicine. The book does not purport to cover the entire field of anoxemia in disease, but it will interest practicing physicians because it reviews our knowledge of the physiologic processes which are fundamental to a proper understanding of many of the phenomena of cardiac and pulmonary disease.

ISAAC STARR.

THE AUTONOMIC NERVOUS SYSTEM; ANATOMY, PHYSIOLOGY, AND SURGICAL APPLICATION: By James C. White, M.D., Assistant Professor and Tutor in Surgery, and Reginald H. Smithwick, M.D., Instructor in Surgery, Harvard Medical School. The Macmillan Company, 1941, second edition, 469 pages, 92 illustrations, \$6.75.

This book is an outstanding and complete treatise on the autonomic nervous system. The presentation is clear, written in easy style, and brought up to the minute. The various aspects of the subject are treated in sufficient detail and with authority that would satisfy the critical and informed reader, and yet the book is excellently suited to the needs of the student. Part I, which comprises a little over a third of the book, is devoted to anatomy, physiology, drugs and hormones, and methods of study. Part II is devoted to the application of basic facts toward the understanding and treatment of diseases and syndromes that have some relation to the autonomic system. Part III gives a clear description of surgical techniques.

Statements are abundantly supported by authorities and complete bibliographies without breaking the sequence of description or making the reading laborious.

Older theories are refreshingly challenged in the light of new data, particularly in reference to the role of the autonomies in pain syndromes.

One of the authors (White), in discussing the transmission of visceral pain in the spinal cord (p. 142), states that it is likely that fibers which transmit such pain ascend, at least in part, in the posterior columns. This conclusion is based on the fact that, in some cases, chordotomy did not abolish the pain of bladder and colon distension. This has not been my experience in the study of over 100 chordotomies. My results indicate that the modality of pain, from whatever source, is mediated through the anterolateral column.

In discussing Raynaud's disease, the authors adhere to Raynaud's original contention that the disease is primarily an abnormality of the sympathetic system, but some very convincing evidence that Raynaud's disease is primarily a vascular abnormality has recently been presented. Lewis was the first to adduce such evidence, and is given credit. Dr. Julius Wolkin and I have recently obtained further evidence (AM. HEART J. 23: 535, 1942) that supports Lewis' contention. This is an important controversy because it implicates other diseases for which the sympathetics have been indicted on grounds that should be questioned.

The subject of essential hypertension is reviewed, and a fair appraisal given of the various surgical methods of treatment which are used at the present time. The authors endorse sympathectomy in the treatment of hypertension in selected cases; their own results have been quite favorable in groups I and II. They feel that bilateral excision of the sympathetic trunks from T<sub>6</sub> to at least L<sub>2</sub>, together with both great splanchnic nerves from the semilunar ganglia to the mid-thoracic level, is the surgical treatment of choice.

The book is obviously the result of a painstaking and thorough digest of the literature by skillful critics who have themselves engaged phases of the subject in significant researches and clinical application.

OLAN R. HYNDMAN.

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